

Leveraging Knowledge-Based Approaches to Promote Antiretroviral Toxicity Monitoring in
Underserved Settings

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Submitted in partial fulfillment of the
requirement for the degree of
Doctor of Philosophy
under the Executive Committee
of the Graduate School of Arts and Sciences

COLUMBIA UNIVERSITY

2017

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ABSTRACT

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As access and use of antiretroviral therapy continue to increase, the need to improve antiretroviral toxicity monitoring becomes more critical. This is particularly so in underserved settings, where patterns of antiretroviral toxicities possibly alter the need for and frequency of antiretroviral toxicity monitoring. However, barriers such as few skilled healthcare providers and poor infrastructure make antiretroviral toxicity monitoring in underserved settings difficult. The purpose of this dissertation was to investigate how standard clinical guidelines, knowledge-based clinical decision support, and task delegation could be leveraged to overcome barriers to antiretroviral toxicity monitoring in underserved settings.

The strategy adopted in this dissertation was guided by the Design Science Research Methodology that emphasizes the generation of scientific knowledge through building novel artifacts. Two qualitative descriptive studies were conducted to characterize the contextual factors associated with antiretroviral toxicity monitoring in underserved settings. Supported by the findings from these studies, a knowledge-based software application prototype that implements clinical practice guidelines for antiretroviral toxicity monitoring was developed. Next, a quantitative validation study was used to evaluate the structure and behavior of the prototype's knowledge base. Lastly, a quantitative usability study was conducted to assess lay health worker perceptions of the satisfaction and mental effort associated with the use of checklists generated by the prototype.

This dissertation research produced empirical evidence about the broad motives and strategies for promoting medication adherence, safety, and effectiveness in underserved settings. It also identified strengths, weaknesses, barriers, facilitators, and process redesign recommendations for antiretroviral toxicity monitoring within ambulatory HIV care workflows in underserved settings. Additionally, it provided evidence about the extent to which antiretroviral toxicity domain knowledge could be implemented in a knowledge-based application for supporting point-of-care antiretroviral toxicity monitoring. Lastly, the research provided previously unavailable empirical evidence about the perceptions of lay peer health workers on the use of checklists for the documentation of antiretroviral toxicities.

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Acknowledgements

This dissertation was made possible through the concerted effort of many people. I would like to express my sincere gratitude to my research advisor, Dr. Andrew S. Kanter, for his continuous guidance, support, and mentorship. I am forever grateful to Dr. Kanter for having faith in me even during my most challenging times. His immense knowledge, insight, patience, and flexibility was instrumental in the realization of this dissertation and in transforming me into a competent scholar. My sincere thanks also go to Prof. Carol Friedman who served as my co-advisor. I feel very fortunate to have tapped into Prof. Friedman's immeasurable wealth of knowledge and experience. I will forever be grateful to her for providing a caring environment and for steadfastly encouraging me to make the most of my potential through hard work, determination, and discipline.

Many thanks also go to Drs. Gilad Kuperman, Lena Mamykina, and Martin Were who served on my dissertation committee. Without their expert advice and insight, this dissertation would not have been possible, and I am sincerely grateful for everything I learned from them. My thanks also go to my friends and colleagues at the Columbia University's Department of Biomedical Informatics. I am particularly grateful to Drashko Nakikj, Silis Jiang, and Fernanda Polubriaginof whose unwavering support and constructive feedback significantly improved my work.

Additionally, I would like to thank the Fulbright Program for honoring me with the Fulbright Science and Technology Fellowship that enabled me to pursue my PhD research. Many thanks also go to Prof. George Hripcsak who was instrumental in ensuring that I had the funds required to complete my dissertation.

Finally, I would like to thank my friends and family for their relentless love and support. My utmost thanks go to my wife Lisper and my daughter Letisha who gave up so much for me to pursue my academic dream.

Chapter 1. Introduction

1.1. Background

With worldwide estimates of 36.7 million people living with HIV, 2.1 million new HIV infections, and 1.1 million deaths from HIV-related illnesses in 2015, HIV/AIDS remains a major global public health challenge [1]. The clinical burden of this incurable disease is particularly important for sub-Saharan Africa which is home to approximately 25.6 million (70%) of the people living with HIV worldwide and accounts for two-thirds of all new HIV infections [1]. Fortunately, the introduction and use of antiretroviral therapy has not only reduced the morbidity and mortality associated with HIV but also improved the longevity and quality of life of people living with HIV [2]. It is for these reasons that the rapid scale-up of antiretroviral therapy in low- and middle-income countries has been hailed as one of the most significant public health intervention in the history of humanity [3].

However, because of improved access to antiretroviral therapy along with the adoption of new guideline recommendations that promote early initiation and prophylactic use of antiretroviral drugs, not only has the number of people using antiretroviral drugs increased but also more users are exposed to these agents earlier and for longer periods [2, 4]. These trends have raised important concerns about the potential increase in the occurrence of antiretroviral toxicities [2, 4, 5]. Antiretroviral toxicities are unintended consequences of antiretroviral therapy. They have been reported with the use of all antiretroviral drugs and may range from mild side-effects such as nausea to life-threatening adverse drug reactions such as renal failure [6]. Antiretroviral toxicities are estimated to occur in 10% of participants in clinical trials [6]. It is plausible that the prevalence of antiretroviral toxicities is much higher outside of clinical trials, particularly in low- and middle-income countries which are the largest consumers of antiretroviral therapy [1]. For example, a

prospective cohort study of 3921 adult HIV patients receiving care at 7 teaching hospitals in Ethiopia reported that antiretroviral toxicities occurred in 22.1% of the participants [7]. Similarly, a prospective Thai cohort study of 417 HIV patients reported major antiretroviral toxicities in 24% of the participants [8]. Although the impact of antiretroviral toxicities remains a research subject, they have been shown to be among the most common reasons for medication non-adherence, treatment substitutions, treatment discontinuation, and loss to follow-up in HIV care [2, 9].

With increased access and use of antiretroviral therapy, there has been a recognized need to improve the monitoring of the safety of these life-saving medications [4, 5]. This is particularly so in underserved settings, where variations in host genetics, environment, behavior, and comorbid disease burdens could influence the range and patterns of antiretroviral toxicities and possibly alter the need for and frequency of antiretroviral toxicity monitoring [10]. Unfortunately, it is plausible that barriers such as few skilled healthcare professionals, poor infrastructure, and limited financial resources make it difficult to implement antiretroviral toxicity monitoring in underserved settings [11, 12]. At the same time, several opportunities for improving antiretroviral toxicity monitoring in underserved settings exist. For example, clinical practice guidelines are important sources of evidence-based knowledge that could be used to meet clinician information needs pertaining to point-of-care antiretroviral toxicity monitoring [2, 6]. Additionally, clinical decision support tools could be used to promote adherence to clinical practice guidelines as well as assist care providers to gather and analyze antiretroviral toxicity data for informed decision-making [13-15]. On the other hand, task shifting, which refers to the delegation of responsibilities to health workers with shorter training and fewer qualifications but who are more readily available [16, 17], could potentially facilitate antiretroviral toxicity monitoring activities such as data collection and patient counseling.

However, despite the fact that opportunities for improving antiretroviral toxicity monitoring in underserved settings exist, key knowledge gaps remain. For example, there is limited information on the quality of current point-of-care antiretroviral toxicity monitoring activities within clinical workflows in underserved settings. Similarly, there is lack of sufficient evidence on the setting-specific facilitators and inhibitors of point-of-care monitoring of antiretroviral toxicities. Also, domain knowledge in clinical practice guidelines that could support clinician reasoning about antiretroviral toxicities is mostly available as textual narratives that are not readily usable as point-of-care interventions. Furthermore, the extent to which clinical practice guidelines could be successfully implemented to support antiretroviral toxicity monitoring using approaches that involve task shifting is not well understood. Additionally, there has been limited research on the pre-implementation evaluation of the HIV care workflows and how these affect the design, integration, function, usability, and feasibility of documentation and decision-making aids for antiretroviral toxicity monitoring in underserved settings. More research is, therefore, needed to provide evidence on the concerted use of clinical guidelines, clinical decision support, and task shifting to improve antiretroviral toxicity monitoring efforts in underserved settings.

1.2. Purpose

The overarching purpose of this dissertation research was to advance the scientific body of knowledge by responding to a number of research questions pertaining to how clinical practice guidelines, knowledge-based clinical decision support, and task shifting could be leveraged to improve the documentation and analysis of antiretroviral toxicities within ambulatory HIV care workflows in underserved settings. The purpose of the dissertation was threefold. First, it aimed at increasing the contextual knowledge of the broad motives and strategies for enhancing medication safety in underserved settings, as well as the specific the barriers to and facilitators of

the documentation and analysis of antiretroviral toxicity within ambulatory HIV care workflows in such settings. Second, it aimed at demonstrating how antiretroviral toxicity domain knowledge and reasoning derived from existing clinical guidelines could be implemented in a knowledge-based application, and how the structure and behavior of the knowledge base of such an application could be validated. Lastly, it assessed the extent to which lay health workers perceive paper-based antiretroviral toxicity symptom checklists generated by the knowledge-based application developed in the dissertation as usable.

1.3. Specific Aims, Research Questions, and Hypotheses

The research strategy adopted in the dissertation was based on the Design Science Research Methodology [18]. This framework describes the key steps followed in the creation of novel artifacts while placing emphasis on the fact that new knowledge is generated in the process of building the artifacts [18, 19]. Figure 1.1 illustrates the research strategy used in this dissertation which consisted of three main aims. The case studies in Aim 1 explored setting-specific factors associated with the monitoring of antiretroviral toxicities in underserved settings. Supported by the findings from these studies, the objectives of an informatics solution to address the problems associated with point-of-care monitoring of antiretroviral toxicities were defined. Subsequently, a knowledge-based software application prototype that implements standard care guidelines for the monitoring of antiretroviral toxicities was developed. The investigations in Aim 2 validated the structure and behavior of the developed prototype's knowledge base to ascertain its functional completeness and predictive accuracy. The investigations in Aim 3 assessed the usability of checklists generated by the developed prototype and intended to be used by lay health workers for documenting antiretroviral toxicity symptoms at the point-of-care. These aims are described further below.

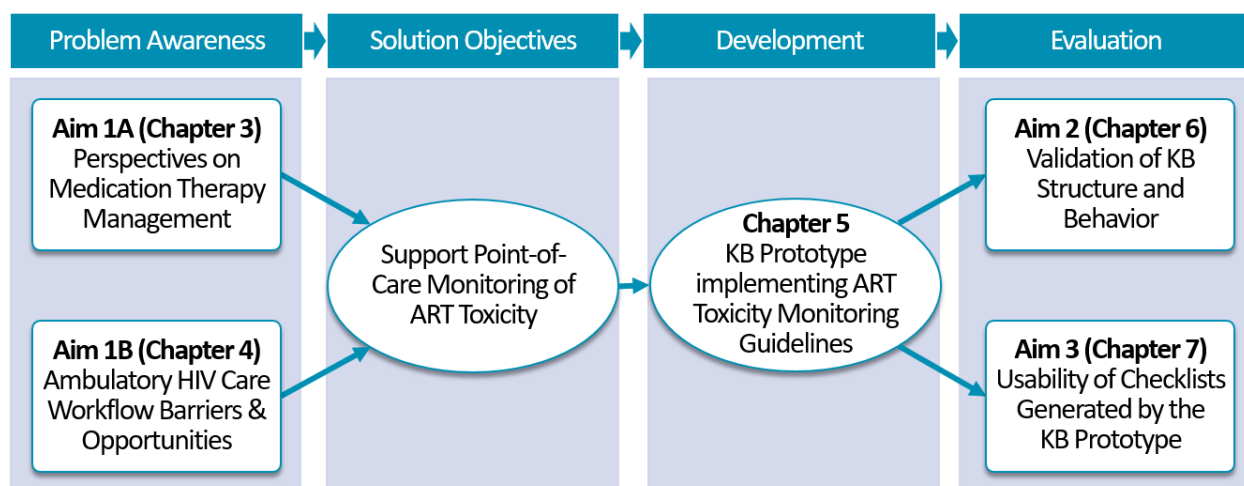


Figure 1.1: Overview of Research Strategy (based on Design Science Research Methodology). ART= Antiretroviral Therapy, KB = Knowledge Base.

Aim 1: Characterize setting-specific factors associated with antiretroviral toxicity monitoring underserved settings

Aim 1A: Assess healthcare provider perspectives on medication therapy management in underserved settings

Medication Therapy Management (MTM) services are professional services that are provided in addition to medication prescription and dispensing to optimize therapeutic outcomes of patients by identifying and resolving drug therapy problems such as medication non-adherence and adverse drug reactions [20]. Unlike in resource-rich settings, little is known about the usefulness of MTM in underserved settings. Additional research is, therefore, needed to provide insight into short-term and long-term strategies for adopting MTM in underserved settings. Given that MTM is a labor- and time-intensive process, it is plausible that its implementation in underserved settings should involve motives backed by local needs, and strategies driven by the necessity to overcome setting-specific challenges such as insufficient personnel. Accordingly, the study in Aim 1A (Chapter 3) explored the perspectives from health providers working in an underserved setting in western

Kenya regarding the provision of MTM services. This was with the overarching goal of identifying the motives and strategies for the implementation of MTM services in underserved settings.

Research Question

- What are the perspectives of healthcare providers based in an underserved setting on the motives and strategies for the provision of MTM services in such settings?
 - To what degree do healthcare providers perceive the task shifting of MTM responsibilities to lay providers as useful?

Aim 1B: Assess ambulatory HIV care workflow patterns in underserved settings

The detection and early intervention of antiretroviral toxicities (side effects and adverse drug reactions) is an important function of any HIV care workflow [2]. However, it is plausible that antiretroviral toxicities are not adequately documented and recognized in ambulatory HIV care workflows based in underserved settings. This is because care providers lack the time and resources required for the labor-intensive antiretroviral toxicity monitoring. Workflow analyses and quality improvement studies could help researchers and other stakeholders identify the key drivers of suboptimal point-of-care antiretroviral toxicity monitoring in underserved settings. Such studies would inform recommendations for change and serve as the basis for the design, implementation, and evaluation of informatics interventions that target ambulatory HIV care workflows in underserved settings [21]. Aim 1B (Chapter 4) of this dissertation examined different aspects of the ambulatory HIV care workflow at an underserved setting in western Kenya, with the overarching goal of identifying barriers to and facilitators of point-of-care antiretroviral toxicity monitoring in underserved settings.

Research Questions

- What constitutes the ambulatory HIV care workflow in an example of an underserved setting?

- *How does information flow among actors and artifacts in the workflow?*
- *What sequential steps constitute the workflow?*
- *What cultural influences affect the execution of the workflow?*
- *How is the workflow organized physically?*
- *What artifacts are important in the workflow?*
- What are the barriers to and facilitators of point-of-care antiretroviral toxicity monitoring in underserved settings?

Aim 2: Validate the structure and behavior of a knowledge base implementing clinical guidelines for point-of-care antiretroviral toxicity monitoring

Based on the findings from the studies in Aim 1, a prototype knowledge-based application that implements clinical care guidelines and that is intended for use in point-of-care antiretroviral toxicity monitoring was developed. In Aim 2 (Chapter 6), the quality of this prototype's knowledge base was evaluated by determining the validity of its structure and behavior. The purpose of the structural validation was to determine if the concept-concept relationships in the prototype's knowledge base were accurate representations of domain knowledge. Structural validation was achieved by determining the proportion of relationships in the prototype's knowledge base that were present in publicly available medication toxicity knowledge bases. The purpose of the behavioral validation was to determine the functional completeness and predictive accuracy of the prototype's knowledge-base in order to ascertain that the prototype behaves as it supposed to. Behavioral validation was achieved by comparing the similarity and accuracy of the detection of antiretroviral toxicities, toxicity risk factors, and toxicity observations between the prototype and human experts.

Research Questions and Hypotheses

- To what extent is the representation of ingredient-condition relationships in a prototype knowledge base implementing clinical guidelines for antiretroviral toxicity monitoring similar to the representation of concept-concept relationships in existing medication toxicity knowledge bases?

- What proportion of paired ingredient-condition relationships in the knowledge base exists in domain knowledge evidence sources?

H₁: At least 80% of the ingredient-condition relationships in the prototype knowledge base are equivalent to ingredient-condition relationships present in domain knowledge evidence sources.

- To what extent are the antiretroviral toxicity reports generated by a prototype knowledge base implementing clinical guidelines for antiretroviral toxicity monitoring comparable to the antiretroviral toxicity reports generated by human experts for a random sample of test cases?

- How similar are antiretroviral toxicity reports generated by the prototype and reports generated by human experts based on the Jaccard distance?

H₁: The mean Jaccard distance between the prototype knowledge base and human experts is different from the mean Jaccard distances among human experts.

- What is the difference in the mean proportion of correct responses per case between reports generated by the prototype and reports generated by human experts?

H₁: There is a difference in the mean correctness of responses per case between reports generated by the prototype compared to reports generated by human experts.

Aim 3: Assess the Usability by Peer Health Workers of Computer-Generated Checklists for Point-of-Care Antiretroviral Toxicity Symptom Documentation

Standard care guidelines recommend a symptom-directed approach to monitoring antiretroviral toxicity at the point-of-care [2]. In this approach, clinicians use their knowledge, skills, and experience to clinically assess signs and symptoms reported by patients and draw conclusions about real and potential antiretroviral toxicities [2, 22]. The symptom-directed approach is, however, time- and task-intensive and may not be successfully adopted in ambulatory HIV care workflows in underserved settings which experience health workforce challenges. At the same time, opportunities exist in the form of shifting of data collection tasks from clinicians to more readily available personnel such as lay health workers [21, 23]. Furthermore, using standardized tools such as checklists, profiles, and scales [24, 25] could improve the quality of data collected through task delegation. However, little is known about the usability of these instruments for collecting antiretroviral toxicity monitoring data and as perceived by lay health workers.

Aim 3 (Chapter 7) investigated the usability of antiretroviral toxicity symptom screening checklists generated by the knowledge-based application prototype developed in this dissertation. The usability investigations assessed the levels of satisfaction and mental effort required to complete the checklists as perceived by lay peer health workers based in an underserved setting. The investigations also identified the usability problems of the checklists that needed to be addressed in future development iterations.

Research Questions

- To what extent do lay peer health workers perceive computer-generated checklists for screening antiretroviral toxicity symptoms as satisfactorily useful and easy to use?

- To what extent do peer health workers perceive the use of computer-generated checklists to document antiretroviral toxicity symptoms as satisfactory?

H₁: The level of peer health worker satisfaction with the use of computer-generated checklists for documenting antiretroviral toxicity symptoms is >68 on the System Usability Scale (SUS), corresponding to above average usability.

- To what extent do lay peer health workers perceive the use of computer-generated checklists to document antiretroviral toxicity symptoms as difficult (cognitively challenging)?

H₁: The median level of mental effort required by lay peer health workers to document antiretroviral toxicity symptoms on computer-generated checklists is <20 on the Subjective Mental Effort Question (SMEQ) scale, implying the task is not very hard to do.

1.4. Significance

Although the clinical significance of antiretroviral toxicities has been well-studied, there is a dearth of literature on strategies for increasing the efficacy and efficiency of antiretroviral toxicity monitoring in underserved settings. Although researchers acknowledge the fact that HIV care programs based in underserved settings have limited capacity to monitor antiretroviral toxicities adequately, little is known about how toxicity monitoring is currently conducted and how these processes could be improved within the constraints of available resources. Furthermore, although standard care guidelines could be useful for enhancing antiretroviral toxicity monitoring in underserved settings, research on automated methods for increasing access to guideline recommendations at the point-of-care in underserved settings remains scarce. Finally, studies on enhancing care guideline adherence through the use of technologies such as mobile health (mHealth) applications have primarily focused on evaluating the impact of the interventions on

clinical outcomes and studies are therefore needed to demonstrate how the usability, feasibility, and workflow integration of such tools can be rigorously evaluated.

The significance of this dissertation research is that it synthesizes the perspectives from healthcare stakeholders based in an underserved setting on the motives and strategies for promoting medication safety and effectiveness in such settings. In so doing, this dissertation research identifies disease focus areas and service provision approaches that could be prioritized in underserved settings. Additionally, this dissertation examines an example of an ambulatory HIV care workflow to identify the key drivers of suboptimal antiretroviral toxicity monitoring in underserved settings. It subsequently provides informatics-based process redesign recommendations that could be adopted to improve the quality of the point-of-care antiretroviral toxicity monitoring in such settings. This dissertation research also examines the extent to which antiretroviral toxicity information available as textual narratives in standard care guidelines and approved drug labels could be coded in a knowledge-based software application using existing medical terminology resources. It also reports the challenges involved in translating textual domain knowledge into a functional knowledge-based application. Lastly, it provides an understanding of the extent to which lay peer health workers based in an underserved setting perceive the use of computer-generated checklists for documenting antiretroviral toxicity symptoms as useful and easy to use. The findings of the studies conducted in this program of research improve the contextual understanding of setting-specific factors associated with the point-of-care monitoring of antiretroviral toxicities in underserved settings. This dissertation research also delineates how the concerted use of informatics innovations, clinical guidelines, and task redistribution could be applied to overcome some of the key barriers associated with monitoring antiretroviral toxicities in underserved settings. The resources developed as part of this dissertation research could prove

useful in improving the antiretroviral toxicity documentation and decision-making in ambulatory HIV care workflows in underserved settings.

1.5. Outline of the Dissertation

This dissertation is comprised of 8 chapters. Chapter 1 introduces the research problem and purpose of the dissertation, outlines its specific aims, research questions, and hypotheses, and highlights its relevance to biomedicine. Chapter 2 presents a review of previously published research that is relevant to the dissertation, assesses knowledge gaps in prior work, and delineates the contributions of the dissertation with respect to the identified knowledge gaps. Chapters 3 and 4 report findings on the exploration of healthcare provider perspectives on MTM (Aim 1A) and the analysis of ambulatory HIV care workflow patterns in an example of an underserved setting (Aim 1B). Chapter 5 describes the objectives and the process of construction of a knowledge-based application prototype that addresses the point-of-care antiretroviral toxicity monitoring barriers identified by the studies conducted under Aim 1. Chapter 6 reports findings from the evaluation of the structure and behavior of the prototype (Aim 2) while Chapter 7 reports findings on the usability of antiretroviral toxicity symptom screening checklists generated by the prototype as perceived by peer health workers based in an underserved setting (Aim 3). Lastly, Chapter 8 discusses the conclusions and future work related to the dissertation.

Chapter 2. Literature Review

2.1. Introduction

This chapter presents a synthesis of the current biomedical literature on antiretroviral toxicity monitoring. It summarizes the clinical significance of antiretroviral toxicity in the context of other drug therapy problems. It describes the current state of knowledge about approaches for identifying, documenting, and reporting antiretroviral toxicities, and highlights the challenges associated with antiretroviral toxicity monitoring in underserved settings. The chapter concludes with a description of the existing knowledge gaps and delineates the contribution of the dissertation in light of the identified gaps.

2.2. The burden of HIV/AIDS

HIV/AIDS remains one of most significant global public health challenge. The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that in the year 2015, there were 36.7 million people living with HIV, 2.1 million new HIV infections, and 1.1 million deaths from HIV-related illnesses [1]. Approximately 78 million people have been infected with HIV, and 35 million have succumbed to the disease since the start of the epidemic. With an estimated 25.6 million (~70%) of all the people living with HIV and accounting for two-thirds of all new HIV infections, sub-Saharan Africa bears most of the clinical burden of HIV disease [1, 26, 27].

The global efforts to scale up access to antiretroviral therapy, especially in low- and middle-income countries, has been hailed as one of the most significant public health intervention in the history of mankind [3]. In the early 2000s, less than 5% of people living with HIV had access to treatment. By 2016, an estimated 18.2 million people, 80% of whom reside in low and middle-income countries, had access to antiretroviral therapy [1]. As a result of the increased access to

antiretroviral therapy, the morbidities and mortalities associated with the HIV infection have been dramatically reduced, and the longevity and quality of life of people living with HIV have been improved [26, 27]. This is exemplified by the fact that between 2000 and 2015, HIV-related mortality rates fell by 28% and new infection rates fell by 35%. The World Health Organization (WHO) also projects that the expansion of antiretroviral therapy to all people living with HIV would avert 21 million HIV-related deaths and 28 million new infections by 2030 [27].

For a long time, the initiation of antiretroviral therapy was based on the World Health Organization (WHO) clinical staging of HIV/AIDS or the CD4 cell count of the patient. It has since been established through clinical trials research that early initiation of antiretroviral therapy not only makes people living with HIV live longer and healthier but also reduces the risk of transmission of HIV [2]. Consequently, clinical practice guidelines for the treatment of HIV infection have been revised to reflect that antiretroviral therapy should be initiated regardless of the clinical stage and at any CD4 cell count for all age groups [2]. The newfound evidence has also led the UNAIDS to set the ambitious 90-90-90 target that requires United Nations member countries to scale up HIV testing and treatment such that by the year 2020, 90% of people living with HIV will know their HIV status, 90% of people diagnosed with HIV infections will receive antiretroviral therapy, and 90% of all people receiving antiretroviral therapy will have viral suppression [28].

2.3. The burden of antiretroviral toxicities

Advancement in antiretroviral therapy has been characterized by the development of more potent and safer antiretroviral drugs and drug classes [6]. For example, less-safe antiretroviral drugs such as didanosine and stavudine have been discontinued from the market, while safer options such as tenofovir, etravirine, and dolutegravir are increasingly being used. Additionally, adherence to HIV treatment has been enhanced by the availability of antiretroviral therapy as fixed-dose combination

products that reduce pill burden and dosing frequency [2, 6]. Also, HIV treatment guidelines are continually revised using evidence from research and observational health data to maximize efficacy, long-term tolerability, and safety of antiretroviral therapy.

Despite the concerted efforts to improve the efficacy and safety of antiretroviral therapy, and although the benefits of viral suppression and immune function improvement outweigh the risks of using antiretroviral therapy, significant challenges associated with the burden of antiretroviral treatment drug therapy problems (DTPs) remain [2, 10]. DTPs are undesirable events or risks involving the use of medications that interfere with the achievement of desired goals of medical care [29]. DTPs have also been described as the actual or potential adverse outcomes resulting from the way in which drugs are used [30]. Some of the most important DTPs associated with antiretroviral therapy include antiretroviral therapy nonadherence, toxicities, and drug resistance [2]. Antiretroviral toxicities are particularly impactful DTPs that have been responsible for a variety of challenges including medication nonadherence, treatment substitution, premature treatment discontinuation, and loss to follow-up among users of antiretroviral therapy [2, 9]. These toxicities may range from mild side-effects to life-threatening adverse drug reactions and have been reported with the use of all antiretroviral drugs. Examples of major types of antiretroviral toxicities include hypersensitivity reactions, hepatotoxicity, pancreatitis, dyslipidemia, rhabdomyolysis and acute kidney injury.

It is fundamental that care providers anticipate and address the threats posed by real and potential antiretroviral toxicities to maximize the benefits of antiretroviral therapy in individual patients. When initiating antiretroviral therapy and monitoring treatment progress, care providers should consider the risk factors of antiretroviral toxicities which may include the individual patient's age, gender, weight, genetics, comorbidities, concomitant medications, and prior medication

intolerance history [6]. They should use the resources at their disposal to enable detection and early intervention of antiretroviral toxicities experienced by individual patients [6]. Such active monitoring of antiretroviral toxicity would improve individual patient's medication experience and quality of life, reduce chances of medication-related morbidities and mortality, and reduce out-of-pocket costs for the patient [20, 29].

At the population level, as HIV treatment policies continue to evolve, not only is the number of people using antiretroviral therapy expected to increase exponentially but also more people are starting antiretroviral therapy earlier and using them for much longer than ever before [1, 2, 28]. It is, therefore, reasonable to expect that as access and use of antiretroviral drugs for the treatment and prevention of HIV increases, problems due antiretroviral toxicity will also increase [31]. This new challenge is particularly important for underserved settings which bear most of the world's HIV/AIDS burden [31], yet exhibit variations in host genetics, environment, behavior, and disease burdens that could influence the range and patterns of antiretroviral toxicities experienced by patients [10, 32].

2.4. Challenges of antiretroviral toxicity monitoring in underserved settings

WHO recommends that as the access to and use of antiretroviral therapy continue to increase, toxicity monitoring becomes an integral component of the HIV clinical care process [2]. Based on evidence from empirical research, the WHO states that routine toxicity monitoring is crucial for providing data on the incidence and clinical significance of major antiretroviral toxicities and their impact on medication adherence, patient outcomes, and retention in care [2, 10]. The WHO further recommends that countries should use standardized approaches to integrating toxicity monitoring into national monitoring and evaluation systems [2]. Additionally, the WHO recommends that

when data is needed to inform policy and improve HIV clinical outcomes, routine monitoring should be complemented by conducting active surveillance studies of toxicity at sentinel sites [2].

According to current WHO guidelines, routine antiretroviral toxicity monitoring should be conducted primarily using a symptom-directed approach where clinicians assess and analyze the clinical signs and symptoms experienced by patients [2, 22]. Laboratory testing is advised but not required for high-risk people using certain drugs [2]. For example, guidelines recommend that abacavir should not be used in the presence of the HLA-B*5701 allele that is associated with abacavir hypersensitivity reaction. However, the absence of HLA-B*5701 testing does not preclude the use of abacavir. The symptom-directed approach to antiretroviral toxicity monitoring is particularly useful in underserved settings which often lack the capacity to perform routine laboratory monitoring [2]. The key antiretroviral toxicity monitoring indicator is the proportion of patients with treatment-limiting antiretroviral toxicities. These are defined as antiretroviral toxicities that cause life-threatening illness, death, hospitalization, disability or result in treatment discontinuation or substitution [2].

Unfortunately, due to a variety of reasons such as poor healthcare infrastructure and competition for scarce human and financial resources, many HIV care programs in underserved settings do not adequately monitor antiretroviral toxicity [5, 11, 12, 16, 33]. The single most important of these challenges is the lack of human resource capacity required to provide such services [11, 12, 16]. Of particular concern is the perennial shortage of skilled health workers in underserved settings. For example, whereas the World Health Organization recommends a ratio of 2300 persons to 1 pharmacist, sub-Saharan countries have as few as 1 pharmacist for 100,000 individuals [11]. This shortage is compounded by high infectious disease burdens, uneven distribution of pharmacists by location (rural vs. urban, high-income vs. low-income countries) and employment areas (private

vs. public), and challenging working conditions [11, 12, 16]. Other cited human resource capacity challenges include the lack of the professional skills, knowledge, and attitudes needed for antiretroviral toxicity monitoring, inadequate regulation, and oversight, and the lack of interdisciplinary collaboration among different healthcare cadres [11, 34].

Among HIV care programs that monitor antiretroviral toxicities, it is plausible that there are variations in the types, methods, and frequency of data collection due to the inadequate adoption of standard data definitions, formatting and reporting [35]. Furthermore, due to time and resource constraints, toxicity data is documented for selected treatment-limiting antiretroviral toxicities and recorded for selected reasons such as switching or discontinuing antiretroviral regimens [2]. These challenges possibly result in antiretroviral toxicity data sparseness as well as aggregation and analysis difficulties. They extend to medication use in other domains and are exemplified by the dearth of biomedical literature on the incidence, prevalence, and clinical significance of medication toxicities in underserved settings.

2.5. Role of task shifting in antiretroviral toxicity monitoring in underserved settings

Solutions proposed to address challenges in the routine monitoring of antiretroviral toxicities in underserved care settings are primarily focused on tackling the healthcare workforce capacity problem. The most commonly reported approach for achieving this goal is task shifting [11, 16, 17]. Task shifting is the rational redistribution of health service responsibilities among health workforce cadres. It often involves the moving of tasks from highly qualified health workers to health workers with shorter training and fewer qualifications, but who are more readily available [11, 16, 17, 36].

An increasingly popular task shifting approach involves redistributing tasks to peer health workers. A peer is a person who has a shared living experience as another person [23]. Consequently, peer

health workers are lay health workers who have similar disease profiles as the persons they care for [37]. In HIV care, peer health workers would be HIV-positive persons who have demonstrated excellence in self-management and medication adherence [38], and who are trained and remunerated by HIV programs to take up HIV care responsibilities such as counseling, educating, and collecting data from other HIV patients [23]. Empirical research evidence from different domains including diabetes and hypertension suggests that task shifting to peer health workers improves clinical data collection, and enhances patient self-management through education and psychosocial support [37, 39, 40]. It is, therefore, plausible that peer health workers who have had adequate antiretroviral therapy training and experience could safely take up data collection responsibilities associated with the routine monitoring of antiretroviral toxicities in underserved settings. However, the documentation and recognition of medication toxicities is a labor- and time-intensive process that requires trained care providers to use their knowledge and skills implicitly in synthesizing information from patient-specific demographic, clinical, laboratory and medication data [29]. Consequently, to meaningfully delegate antiretroviral toxicity monitoring documentation tasks to peer health workers, such task shifting should be complemented with adequate decision-making aids that reduce the cognitive burden associated with this activity.

It is worth noting that task shifting approaches are not intended to replace standard clinical care delivery. In fact, guidelines and recommendations on task shifting stress that such strategies should be implemented alongside long-term strategies that aim at increasing the total number of qualified health workers in all cadres [17]. Researchers have suggested that long-term strategies for mitigating health workforce challenges should include training of more pharmacists and the extension of pharmacy training curricula to other healthcare cadres [11, 41]. However, the outcomes of these proposals remain unknown. For example, many low- and middle-income

countries continue to face shortages of qualified health workers and rural-urban distribution imbalances despite overall increases in the health workforce. Additionally, many low- and middle-income countries still lack the capabilities, infrastructure, and political will to train health workers in sufficient numbers required to serve their populations adequately [42].

2.6. Role of Informatics in antiretroviral toxicity monitoring in underserved settings

Integrated access to clinical data, information, and knowledge is critical for problem-solving and decision-making during healthcare delivery. The implementation of health informatics and health information system interventions in underserved settings such as those in sub-Saharan Africa has the promise of not only enhancing the quality and efficiency of healthcare delivery but also improving intermediate and clinical outcomes in different disease domains [43]. Due to the ubiquity of mobile phones, a majority of health informatics interventions in underserved settings are mobile Health (mHealth) implementations that leverage the use of mobile phones by patients and care providers [44-46]. A majority of mHealth interventions in underserved settings primarily aim at improving patient medication adherence through the use of patient reminders [47-51], patient education [47, 52], and psychosocial support [48]. Other interventions have aimed at enhancing adherence to clinical guidelines by health workers through alerts and decision aids [13, 14, 53]. Some mHealth interventions have primarily targeted infectious disease such as HIV/AIDS [48, 49, 54, 55], malaria [50, 53], and tuberculosis [51], while others have targeted non-communicable diseases such as diabetes [47, 52, 56] and hypertension [57]. MHealth services are delivered through a variety of media. These include short message service (SMS) where users communicate unilaterally or bilaterally through text messages [48-50, 54, 58], interactive voice response (IVR) where users interact with pre-recorded tailored messages [54, 57], smartphone applications that capitalize on graphics, videos and audios [52], or a combination of different

modalities such as SMS and IVR [55, 59]. There is no consensus on the standard delivery medium for use in underserved settings [48, 60], but research findings suggest that the information content and structure, as well as the frequency of information delivery, could affect the patient engagement and eventual outcomes of interventions [48].

The use of informatics interventions in underserved settings have been associated with improved process outcomes such as data quality and accuracy, health behavior and self-efficacy, and care provider adherence to guidelines [15, 46]. For example, Were et al. showed that the use of paper clinical summaries generated from patient electronic health records improved the quality of care by allowing providers to spend more time in the direct care of patients and by reducing the length of patient visits [61]. Both Amoroso et al.[62] and Allen et al.[63] report reductions in data errors associated with the use of OpenMRS, an open-source medical record system widely used in underserved settings [64]. With respect to improved health behavior, a randomized control trial by Pop-Eleches et al., 53% of patients in receiving weekly SMS reminders were adherent to their medications compared to 40% in the control group [48]. Similarly, in a randomized control study by Lester et al., the relative risk of medication non-adherence was lower among participants receiving weekly SMS interventions compared to standard care [49]. In a randomized control trial comparing patient education via a tablet (iPad) application to printed educational material, Heisler et al. found an improvement in knowledge about diabetes albeit with no discernible differences between the comparison groups [52]. With respect to guideline adherence, Were et al. demonstrated a fourfold increase (85% intervention versus 18% control) in the completion of overdue tasks such as ordering CD4 tests when clinicians use computer-generated reminders in pediatric HIV care [14]. Similarly, a cluster randomized control trial of 2269 children with malaria by Zurovac et al. found that guideline-based case management improved by 24% among

community health workers using SMS reminders compared to the control group. Findings from clinical trials show that mHealth and other informatics interventions improve clinical outcomes in underserved settings, although additional evidence is desired. For example, the randomized control trial by Lester et al. also showed that weekly SMS intervention reduced the relative risk of virologic failure [49].

Unfortunately, there is limited empirical evidence on use and impact of mHealth and other informatics interventions for supporting antiretroviral toxicity monitoring in underserved settings. However, most of the knowledge gained from the studies highlighted above can be extrapolated to the antiretroviral toxicity domain. For example, the use of mHealth is an attractive approach for the off-site communication with patients in underserved settings. Interventions could, therefore, be developed to enhance the remote collection of antiretroviral toxicity data from patients, and communication of standard care recommendations to patients as well as care providers.

The broader challenges associated with the use of informatics interventions for supporting antiretroviral toxicity monitoring would be similar to previously reported challenges. Deployment would be hindered by barriers such as lack of stable electricity, lack of stable internet connection, and lack of a workforce that can support the technologies [43]. Also, data collection and information presentation would be limited by the available technology [46, 57]. For example, IVR technology only allows interaction via coded voice messages and dialed responses, while SMS technology only allows communications through text and simple multimedia messages. Additionally, if mobile phones are used to for patient-centered interventions, then privacy and confidentiality concerns must be taken into consideration as shared ownership of mobile phones are common in many households in underserved care settings [60, 65]. Lastly, the trade-offs between the use of electronic data capture devices at the point-of-care versus the use of paper data

collection forms with retrospective data entry should be considered [43]. For example, compared to the use of paper forms, the use of electronic data collection systems at the point-of-care could result in faster, cheaper, and more accurate data entry [66]. On the other hand, users of electronic data entry devices could perceive them as disruptive and unreliable at the point of care [67, 68].

2.7. Knowledge Gaps

Enhancing the symptom-directed approach for monitoring antiretroviral toxicities in underserved settings would require the concerted use of task shifting and integration of record-keeping and decision-making aids. However, given that this is a relatively new paradigm, several knowledge gaps exist in this domain. For example, little is known about how the guideline-recommended symptom-directed approach for antiretroviral toxicity monitoring would be implemented in underserved settings to optimize treatment outcomes. The key relationships among the structures, processes, and outcomes of the symptom-directed approach are not well understood. It is not obvious how setting-specific factors such as practice paradigms, users, clinical workflows, and facility characteristics would influence the quality of symptom-directed antiretroviral toxicity monitoring, as well as the design, implementation, and evaluation of technologies that support this approach.

Furthermore, to standardize documentation, analysis, and reporting of antiretroviral toxicities, it is important that record-keeping and decision-making aids for antiretroviral toxicity monitoring in underserved settings rely on standardized medical vocabulary. However, little is known about how unstructured domain knowledge could be characterized and organized to facilitate automated reasoning about antiretroviral toxicity.

Another important consideration is the fact that software applications developed to support antiretroviral toxicity monitoring in underserved settings are likely to be used by multiple users

including professional and lay health workers. As such, it is important to determine the usability and feasibility of the use of such tools across different cadres of care providers. In particular, there is a need to ascertain that antiretroviral toxicity monitoring tasks can be effectively redistributed to lay health workers. The extent to which this cadre comprehends medical terminology used within the antiretroviral toxicity domain should be determined.

2.8. Contributions of the Dissertation Research

In light of the knowledge gaps described in the previous section (2.7), this dissertation research has several contributions. First, a qualitative descriptive study was used to explore the perspectives of healthcare providers on the provision of MTM services in underserved settings (Chapter 3). This contributes to the broad understanding of the motives and strategies for promoting medication adherence, safety, and effectiveness in underserved settings. Second, a workflow analysis and quality improvement case study was conducted to investigate ambulatory HIV care workflow patterns in an example of an underserved setting (Chapter 4). In so doing, the dissertation contributes to the contextual knowledge of barriers and facilitators of point-of-care antiretroviral toxicity monitoring in underserved settings through the concerted use of guideline-based decision support and task redistribution. It also demonstrates how graph models and business process model notations can be used to model and visualize different aspects of workflows in underserved settings.

At the core of this dissertation research was the development and evaluation of a knowledge-based application implementing guidelines for antiretroviral toxicity monitoring. In conducting this work, the dissertation demonstrates how concepts and relationships within the antiretroviral toxicity domain can be characterized using currently existing biomedical terminology resources and implemented in a knowledge-based software application (Chapter 5). It also demonstrates how

informatics approaches could be used to validate the structure and behavior of such knowledge-based applications (Chapter 6).

Finally, the dissertation investigated the usability of computer-generated checklists for documenting antiretroviral toxicity symptoms as perceived by peer health workers (Chapter 7). These investigations contribute to knowledge on specific challenges associated with redistributing data collection tasks to peer health workers. The investigations also contribute to a better understanding of the desired content and functionalities of checklists for monitoring antiretroviral toxicities as perceived by lay health workers.

Chapter 3. Assessing healthcare provider perspectives on medication therapy management in underserved settings

3.1. Introduction

Medication Therapy Management (MTM) services are non-dispensing services that optimize therapeutic outcomes for patients by identifying and resolving drug therapy problems such as nonadherence, adverse drug reactions, and subtherapeutic dosing [20]. MTM services are distinct from but complementary to routine medication prescribing and dispensing activities. MTM services are the embodiment of the philosophy of pharmaceutical care [69, 70]. This philosophy asserts that it is the responsibility of the pharmacist to meet all drug-related needs of the patient, to be held accountable for those needs and to assist the patient in achieving his or her therapeutic goals through collaboration with other health professionals [29].

A commonly used framework for the provision of MTM services is the *MTM Service Model in pharmacy practice* [69]. The model describes five core elements necessary for MTM service provision. These are described as follows. *Medication therapy review* refers to the systematic process of collecting patient-specific information, assessing treatments to identify medication-related problems, developing a prioritized list of the problems, and creating a plan to resolve them. The *personal medication record* is a comprehensive list of the patient's medications including prescription, non-prescription, herbal products and dietary supplements with instructions specified for each drug. This record also contains the patient's demographic data, allergies, and emergency contact information. It is provided to the patient as a guide for medication self-management. The *medication-related action plan* is an individualized list of actions used by the patient to track self-management progress. *Interventions and referrals* are actions taken by an MTM service providers to solve a patient's problem directly or through consultation with other care providers. Lastly,

documentation and follow-up refer to the record-keeping and monitoring activities of MTM service provision necessary for facilitating communication among care providers, billing justification, and in evaluating care progress and outcomes.

Possibly because the provision of MTM services is a relatively new paradigm of pharmacy practice, its implementation in underserved settings is not sufficiently described in the biomedical literature. Nonetheless, it is reasonable to expect that the shortage of healthcare workers, high disease burdens, and limited financial resources could be important barriers to the adoption and scale-up of MTM services in such settings [11, 12]. Concurrently, the acceptance of task shifting as a solution to health workforce challenges [11, 16, 17, 36], and the increased penetration of electronic health records and clinical decision support [15, 46] present valuable opportunities for alleviating barriers to the adoption of MTM services. However, more studies are required to fill in knowledge gaps about the motives, strategies, and constraints associated with the provision of MTM services in underserved settings.

It is plausible that the provision of MTM services in underserved settings would involve motives backed by local needs, and strategies driven by the necessity to overcome setting-specific challenges. Accordingly, the purpose of the study described in this chapter was to explore the perspectives from health providers working in an example of an underserved setting regarding the provision of MTM services. This was with the overarching goal of identifying the motives and strategies for implementing MTM services in similar underserved settings, and determining the degree to which healthcare providers perceive the task shifting of MTM responsibilities to lay health workers as useful. The study involved the use of focus group discussions and individual online surveys with key stakeholders identified through social network analysis.

3.2. Methods

3.2.1. Study Design

A qualitative descriptive study combining the focus group interview and the online survey designs was applied to address the research questions in this study. Social network analysis was used to identify potential participants of the subsequent focus group discussion and online survey. A social network is a group of collaborating or competing entities that are related to each other in a common environment [71]. Social network analysis is the quantitative characterization of the interaction patterns between the entities in a social network [72]. This technique was used in this study because it is thought to be superior to the traditional methods of identifying stakeholders through organizational charts as it captures more complex interactions among people as they conduct their work [73, 74]. The focus group interview was used to gather care provider views on the broad motives and strategies of MTM service provision in underserved settings. The focus group design was chosen because it allows participants to stimulate the thoughts and build upon the contributions of each other, thereby increasing breadth and depth of the discussion [75]. The online survey was used to ascertain the consistency of findings generated by the focus group interview and to identify key stakeholder perspectives on the goals and priorities of implementing MTM in underserved settings. The method was chosen because it enables faster and easier collection of a wider range of potential responses that may not be obtained through consensus-based approaches such as focus group discussions [76].

3.2.2. Setting

This study was conducted at the Academic Model Providing Access to Healthcare (AMPATH) in Eldoret, Kenya. AMPATH is an umbrella healthcare organization formed as a result of the collaboration between Moi University College of Health Sciences, Moi Teaching and Referral

Hospital and a consortium of North American Academic Medical Centers led by Indiana University School of Medicine [77]. AMPATH provides care to both urban and rural patients at its primary site in Eldoret, Kenya and via satellite clinics scattered around western Kenya. Since its inception in the year 2001, and by the year 2016, AMPATH had provided care to about 180,000 HIV/AIDS patients, with almost 2,000 new HIV patients being enrolled each month [78]. The organization expanded its initial clinical focus beyond HIV/AIDS care to encompass chronic disease management, primary healthcare, and specialty healthcare. To address the healthcare workforce challenge brought about by this scale up, AMPATH is actively researching and implementing task redistribution to other health professionals, lay or community health workers and patient peers [79-81]. To complement these strategies, AMPATH develops documentation and decision support tools to aid care providers with record-keeping and decision-making [82, 83].

3.2.3. Subject Selection

This study targeted medical doctors, clinical officers, nurses, pharmacists and pharmacy technicians who routinely provide a variety of specialized services including clinical assessment, prescribing, dispensing and patient monitoring in the study setting. Social network analysis [72, 73, 84] was used to identify the subjects who most commonly addressed the medication-related needs of patients at the study setting. A self-report survey was administered to a purposive sample of 45 care providers working in the study setting to collect data for social network analysis. In the survey, each respondent indicated interactions with his/her colleagues by answering 3 main questions: 1) Please name up to 5 colleagues you consult whenever you have questions about a patient's medication-related problems. 2) How often do you contact each person? 3) How would you rank the value of the advice you receive from each person? Thirty-seven care providers completed the survey, giving a response rate of 82%. The survey responses were used to create a

social network graph which consisted of 70 nodes (stakeholders) and 181 edges (relationships based on consultations about medication-related problems). This graph was subsequently analyzed to identify potential participants of the focus group discussion and the online survey. The procedure, analysis, and findings of this subject selection process are provided in Appendix 3.1.

3.2.4. Data Collection

A focus group discussion involving 7 stakeholders identified from the social network analysis subject selection process was conducted. Participants of the discussion included 2 pharmacists, 3 pharmacy residents, and 3 pharmacy technicians. The discussion was guided using pre-specified questions that targeted several aspects of the provision of MTM-related services at the study setting (Appendix 3.2). In brief, the questions pertained to identifying healthcare provider perceptions of the achievements, barriers, and challenges of the MTM-related processes in the study setting, and the approaches that could be used to enhance the provision of MTM services in the setting. Examples of key focus group questions include: 1) What are some of the barriers and challenges of the medication use process at AMPATH? 2) What are some of the approaches through which Medication Therapy Management Services can be offered at AMPATH? 3) Please envision the use of an information system that supports the provision of medication therapy management services. What functionalities would you desire in such a system? The discussion was audio-recorded and transcribed.

Eight key stakeholders selected via social network analysis but who had not participated in the focus group discussion responded to an online survey administered via Google Forms. The respondents included 3 pharmacists, 1 pharmacy resident, 1 clinical officer (same as a physician assistant in the United States), and 3 pharmacy technicians. The survey questions and response options were based on the key findings generated from the focus group discussion. The survey

required participants to respond to 5-point Likert items, multiple-answer questions, multiple choice questions, and free text answer questions (Appendix 3.3). Examples of questions in the survey include: 1) Please indicate your level of agreement with respect to whether the following patient groups need more rigorous medication therapy management services; 2) Please select the top THREE patient groups that you think need more rigorous medication therapy management services; 3) What is the single-most-useful approach for providing medication therapy management services in a resource-constrained setting? (Please choose one); 4) Please provide any comments about the role of health information technology on the provision of medication therapy management services in a resource-limited setting.

3.2.5. Data Analysis

Transcripts from the focus group discussion and free text responses from the online surveys were uploaded to Qualitative Analysis Minier Lite, a free qualitative analysis software by Provalis Research [85]. The transcripts were analyzed thematically using the guide proposed by Braun and Clarke [86]. The goal of the analysis was to discover semantic themes within the data that describe an accurate account of the “who, what, why and how” [87] of MTM service delivery in a resource-limited setting. Specifically, the analysis aimed at exploring the participant perspectives on why MTM was necessary, who needed the services, what components were required to deliver the service, and how the services would be delivered. Procedurally, the transcript data were coded to identify important semantic features of the data. The codes were collated into potential themes. These themes were then reviewed against the coded extracts as well as the entire dataset. Each theme was defined and refined, and a report of the findings produced.

Categorical responses from the online surveys were analyzed quantitatively. Likert items were analyzed by determining the most frequent responses option (among Strongly Disagree, Disagree,

Neutral, Agree, and Strongly Agree). The Krippendorff's alpha [88] and the intra-class correlation coefficient type ICC(2,k) [89] were computed to assess the consistency of agreement among survey respondents. Multiple-answer and multiple-choice questions were analyzed by determining the frequencies of selected response options.

3.3. Results

3.3.1. Qualitative Analysis

Thematic analysis of the focus group discussion transcripts and online survey text responses revealed 7 themes under 4 analytic question topics. These themes, along with the example support statements are described in Table 3.1. There were no significant differences of opinion across the different work roles of the respondents.

Why are MTM services needed?

The respondents opined that MTM services should be provided to evaluate and document medication adherence, safety, and effectiveness (Theme 1). This theme falls under a broader theme of the need to promote positive patient outcomes. For example, one participant noted that more rigorous MTM services would have helped avert the side effects and adverse drug reactions that had been previously witnessed in patients receiving care at the setting. Additionally, the participants also reported that MTM services would particularly be significant in countering the increase in the likelihood of the occurrence of medication-related problems as their organization continues to expand its clinical scope of work and care for more patients. Accordingly, the scalability of services without adequate MTM would present new challenges associated with medication use.

Table 3.1: Key themes and example support statements about Medication Therapy Management (MTM) identified from study transcripts

| Topic | Theme | Example Support Statement |
|---|---|---|
| Why is MTM necessary? | 1.MTM is provided to improve patient outcomes by ensuring medication adherence, safety, and effectiveness | <ul style="list-style-type: none"> • “...MTM would ensure that patients stick to set goals and would also provide an effective way of assessing patient outcomes...” [Focus group participant 3, pharmacy resident] • “...some patients endure extended periods of side effects and adverse drug reactions that could easily have been identified earlier and averted.” [Focus group participant 5, pharmacist] |
| | 2.Eligibility is influenced by risks posed by inadequately treated infectious disease | <ul style="list-style-type: none"> • “Newly initiated ART patients will benefit the entire population the most if they are adherent to their medications. This is because if these patients can maintain a low viral load, they have a very low chance of transmitting the virus....” [Survey respondent 3, pharmacist] |
| Who needs MTM services? | 3.Eligibility is influenced by the complexity of treatment, the risk of non-adherence, and the potential for adverse drug reactions | <ul style="list-style-type: none"> • “I think we have a large number of old patients who are on so many drugs. For example, they could be on drugs for their cardiac issues, and they also take drugs for hypertension, arthritis, Alzheimer’s disease, etc.” [Respondent 1, pharmacy resident] • “Newly-initiated patients are most likely going to get lost to follow-up as it takes a while for patients to accept their status. They are also the ones who we need to watch out for adverse drug reactions the most”. [Survey respondent 7, pharmacist] |
| | 4.MTM delivery is influenced by the provider’s perceptions of having the knowledge, skills, and time to provide the services adequately | <ul style="list-style-type: none"> • “The services would require a lot of skilled and educated labor too.” [Focus group participant 4, pharmacy technician] • “High patient volume and low staffing easily tire service providers leading to poor service delivery.” [Survey respondent 6, clinical officer] |
| What is required for MTM service delivery? | 5.MTM delivery is influenced by the patient’s ability and willingness to self-manage and engage in the process | <ul style="list-style-type: none"> • “I think the patient's willingness to be able to listen to advice is a concern. Some patients just perennially in a hurry. Some of them still try to protect their identities, while some remain stigmatized throughout their care. Such patients often than not just demand their drugs and go without counseling.” [Focus group participant 3, pharmacy resident] |
| | 6.MTM activities should be supported by documentation and decision-making aids | <ul style="list-style-type: none"> • “...I think technology can be used to implement protocols effectively and provide accountability.” Focus group participant 7, pharmacy technician • “...information technology is important in helping generate and disseminate information relating to a patient.” [Survey respondent 6, clinical officer] |
| How should MTM be delivered? | 7.MTM approaches should consider human resource challenges and incorporate social capital | <ul style="list-style-type: none"> • “Peers are very efficient at trying to get the truth out of the patients because of the level of trust and the nature of their relationship with the patients” [Focus group participant 5, pharmacist] • “Peers seem to have a better understanding [of the patient] because of past experiences which may be similar to what the patient is having.” [Survey respondent 6, clinical officer] |

Who needs MTM services?

Some respondents opined that patients whose inadequately-treated infectious disease states pose a public health risk of disease transmission should be targeted for MTM services (Theme 2). Proponents of this view believed that high-risk disease cohorts included adult HIV patients who are sexually active and patients with tuberculosis whose adequate treatment was essential for infection control and prevention. Other respondents thought that patients using complex medication regimens would benefit the most from MTM services (Theme 3). They provided examples of cohorts such as multi-morbid chronic disease patients, geriatrics, pediatric patients, and patients on second-line, third-line or salvage HAART and argued that these groups were prone to medication non-adherence. Additionally, some respondents opined that patients at risk of adverse drug reactions would be good candidates for MTM services (Theme 3). Supporters of this view argued in favor of focusing MTM services to HIV patients newly initiated on antiretroviral therapy because this group was prone to nonadherence, was most likely to develop adverse drug reactions, and was likely to be overburdened by the transition to lifelong use of medications.

What is required for MTM service delivery?

From the participants' responses, it emerged that the delivery of MTM service was dependent on three main components. First, MTM service providers needed to have the required knowledge, skills and time to provide MTM services adequately (Theme 4). In this regard, the respondents identified the lack of sufficient training and high patient-to-provider ratios as important staff-related barriers to the provision of MTM services. Task shifting, adequate training, and continuing education were perceived to be the fundamental solutions for mitigating the human resource challenges.

The second component necessary for the provision of MTM services identified from the participants' responses was the patient's willingness and ability to participate and actively engage in the process (Theme 5). The respondents thought that patient engagement was essential for MTM service delivery particularly because the service was patient-centric. They identified patient passivity and stigma, predominantly among HIV patients, as key patient-related barriers to patient engagement. The respondents were concerned that some patients left all care-related decision-making to the healthcare provider. They argued that such patient passivity and disempowerment would inadvertently make the provision of MTM services difficult. Furthermore, the respondents noted that because of the fear of disclosing their status and being stigmatized, most patients kept their treatment information highly confidential. Consequently, MTM requirements such as the need for patients to keep self-management records would not be popular among patients. Patient counseling and education during clinic visits were perceived to be suitable approaches for improving patient engagement and self-efficacy.

The respondents opined that the third key component necessary for MTM service delivery was an information system that supports documentation and decision-making (Theme 6). The respondents thought that health information technology (IT) would enable MTM service providers access and communicate patient information in a timely manner. They also opined that the use of decision support systems could enhance care provider adherence to protocols and guidelines. Some respondents, however, cautioned that the implementation of health IT would introduce additional overhead costs associated with the need to train users and maintain such systems. Additionally, some respondents were concerned about the possibility of health IT solutions diminishing human patient-provider interactions.

Table 3.2: MTM service provision approaches stratified by care provision strategy and setting

| | | Cadre | | |
|--|----------------|----------------------------------|----------------------------------|----------------------------|
| | | Professional | Task-shifted | Hybrid |
| | Setting | | | |
| | Single-Patient | Professional Single-Patient Care | Task-shifted Single-Patient Care | Hybrid Single-Patient Care |
| | Group | Professional Group Care | Task-shifted Group Care | Hybrid Group Care |

How should MTM services be delivered?

Six MTM care provision approaches emerged from the qualitative analysis of respondent discussions on MTM strategies for underserved settings. These approaches were related to the cadre of the MTM service provider and the setting in which the MTM service was delivered (Table 3.2). The six approaches were labeled professional single-patient care, task-shifted single-patient care, hybrid single-patient care, professional group care, task-shifted group care, and hybrid group care. There was no consensus on the single most useful approach for the delivery of MTM services, but a majority of the respondents opined that successful approaches should overcome workflow challenges through strategies that also explore the benefits of social capital (Theme 7).

In the professional approaches, MTM services would be delivered by a trained and qualified professional as the sole care providers. Proponents of these approaches stated that adequately trained and skilled professionals could provide MTM services to most patients regardless of the patient's disease state(s) and the complexity of their management. Opponents of the professional

approaches argued that although the approaches would be desirable, workforce challenges would limit their utility in underserved settings (Theme 4).

In the task-shifted approaches, all responsibilities of providing MTM services would be redistributed from professional to more readily-available non-professional health care workers. A predominant view among the proponents of this approach involved the use of lay care providers with similar disease experiences as the patients they care for (called peer health workers) in the provision of MTM services. Arguments in favor of using trained peer health workers as the primary MTM service providers included the fact that patients would be more open to care providers who have had similar experiences as they have (Theme 7). This openness would be useful in combating passivity and stigma, particularly in HIV. Counter-arguments against task shifting MTM responsibilities to lay health workers included overhead costs associated with selecting and training the care providers, the inability of the care provider to manage complex cases, and the possible lack of acceptance by professionals.

In the hybrid approaches, both professionals and non-professionals would share responsibilities in the provision of MTM services. Proponents of these approaches stated that they would capitalize on the advantages of both the professional and the task-shifted approaches. For example, lay MTM service providers would handle cases that were simpler but more common, freeing up time for professionals to handle the fewer but more complex cases. Alternatively, professionals would remain as the primary MTM service providers, but the lay health workers would take up some responsibilities that are easy but time-intensive such as data collection, patient counseling, and patient education. This would free up time and resources for the professionals to focus on more cognitively-demanding tasks such as analyzing MTM information and making care decisions.

With respect to the care provision setting, the proponents of group-based approaches opined that these approaches would be cost-effective and efficient since care is delivered to multiple persons at the same time. They also argued that group-based approaches would provide opportunities for patients to learn from and support each other. However, opponents of the group-based approaches cautioned that the approach might compromise patient privacy and confidentiality and argued that such approaches may only be suitable for non-stigmatizing chronic noncommunicable diseases such as diabetes and hypertension.

3.3.2. Quantitative analysis

All the 8 survey respondents provided responses to 31 Likert items pertaining to findings of the focus group discussion. A majority of the respondents agreed with most of the findings (Figure 3.1). There was reasonable consistency amongst the agreements as was evidenced by a Krippendorff's alpha score 0.355 indicating fair agreement between raters, and an ICC(2,k) score of 0.79 (95% CI, 0.66 to 0.88, $P < 0.001$) indicating moderate to a strong average agreement.

One respondent disagreed, and 2 respondents remained neutral with respect to providing MTM services through task shifting to lay health workers. Similarly, 1 respondent disagreed, and 2 respondents remained neutral with respect to the finding that the lack of skilled providers would be a barrier to MTM service provision in underserved settings.

Interestingly, 4 of the 8 respondents disagreed with the finding that language and communication could be a barrier to the provision of MTM services in an underserved setting, and one respondent remained neutral. Also, while all participants were either neutral or in agreement with the finding that the use of alternative medicines by patients would be a barrier to the provision of MTM services, one respondent disagreed that the matter should be addressed as a goal of providing MTM in underserved settings.

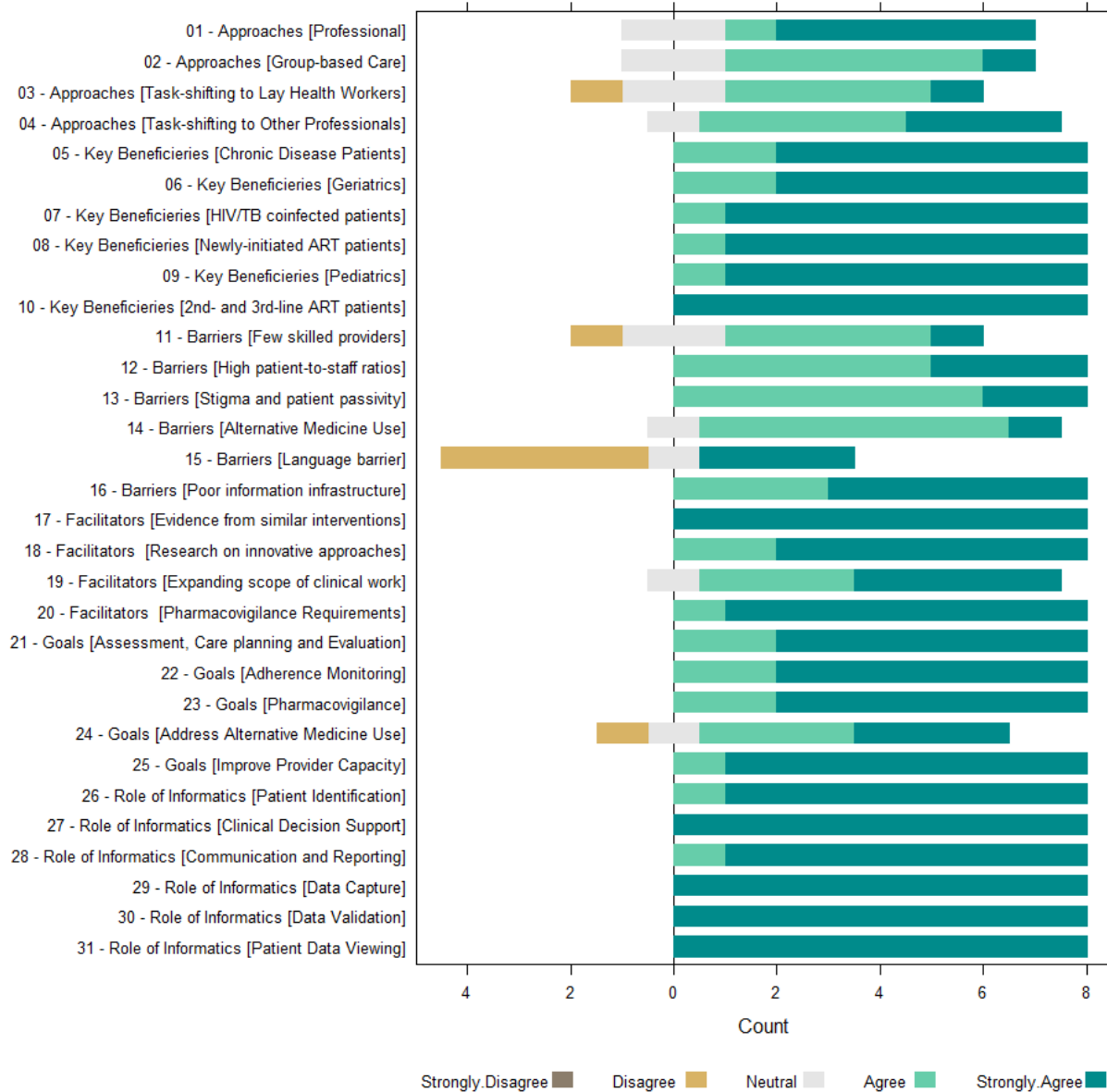


Figure 3.1: Diverging stacked bar chart of responses of 8 stakeholders to 31 Likert items pertaining to findings of a focus group discussion on the approaches, beneficiaries, barriers, facilitators, goals, and the role of informatics in the provision of medication

When asked to identify the top three MTM approaches that would be feasible for an underserved setting, 6 respondents selected both the peer-based and group-based approaches among their choices. Five respondents included the professional approach among their choices. When asked to

identify the single most feasible MTM service delivery approach, task shifting to lay health workers and group-based care tied for first place with 3 respondents selecting each approach. The professional and task shifting to other professional approaches were each selected once.

When asked to identify the top three patient types that are most likely to benefit from pharmaceutical care in the resource-limited setting, all the 8 respondents included HIV patients newly initiated on antiretroviral therapy among their choices. Six respondents included HIV and Tuberculosis comorbidity among their top three choices. When asked to identify a single patient group that would benefit from MTM, 5 respondents selected HIV patients newly initiated on antiretroviral therapy, 2 selected HIV and Tuberculosis comorbid patients and 1 selected chronic disease patients. No respondents selected geriatrics, pediatrics or patients on second-line, third-line or salvage antiretroviral therapy.

3.4. Discussion

The purpose of this study was to identify health care provider perspectives on the motives and strategies of the provision of medication therapy management (MTM) services in underserved settings. To meet the objective of the study, qualitative data from a focus group discussion and an online survey with stakeholders based in an example of an underserved setting were analyzed. The analysis yielded several themes pertaining to the provision of MTM services in underserved settings. There is a dearth of prior research on this subject, and this study can be viewed as a means of generating exploratory findings that could be investigated further.

The findings of this study suggest that the motivations for providing MTM services in underserved settings are similar to those previously described in the literature. By definition, MTM is a service provided to optimize the therapeutic outcomes of individual patients by improving medication

adherence, safety, and effectiveness [20, 29, 90]. The themes about why MTM is necessary for underserved settings that were identified in this study are in line with what is known about these goals of MTM. Additionally, the findings of this study suggest that in underserved settings, HIV patients newly initiated on antiretroviral therapy were most likely to benefit from MTM services. Furthermore, the findings of this study suggest that the provision of MTM services in underserved settings could be motivated by the need to promote population-level infection control and prevention by mitigating risks of suboptimal use of medications among persons with infectious diseases such as HIV and tuberculosis. This particular theme has not been emphasized by previous researchers. A plausible explanation for the lack of emphasis on the theme is that a majority of research on MTM is primarily conducted in high-income settings where infectious disease burdens are lower compared to the low-resource setting in which this study was conducted.

Interestingly, this study reveals several strategies that could be used to provide MTM services in underserved settings. The qualitative analysis conducted in the study discerned six patterns based on the cadre of care provision (professional vs. task-shifted vs. hybrid) and the setting of care provision (single-patient vs. group). Although the findings of this study did not reveal a single strategy that would be optimal for providing MTM services in underserved settings, a recurrent theme was that successful strategies needed to overcome health facility barriers associated both human resource capacity and patient engagement challenges.

It is well-known that one of the key healthcare delivery barriers in underserved settings is the shortage of skilled service providers [11, 12, 16]. Consequently, and as suggested by the findings of this study, the professional single-patient care approach identified by this study and equivalent to conventional MTM service provision [20] would be desirable but unlikely to be sustainable in underserved settings. The training of more professionals is a reasonable long-term solution that

would improve the pool of skilled providers in underserved settings [11, 91]. However, research has shown that despite increases in the number of professional care providers in underserved settings, workforce challenges in these settings are likely to persist due to uneven distribution of health workers with respect to location (rural vs. urban, high income vs. low-income countries) and employment areas (private vs. public) [12, 92].

This study suggests that a task shifting model in which professional MTM service providers team up with other professional or lay health workers to share MTM responsibilities would be a reasonable approach for overcoming workforce challenges associated with the provision of MTM services in underserved settings. The fact that task shifting is a recommended strategy used to enhance healthcare delivery in low- and middle-income countries [16, 17, 36] implies that the hybrid model described in this study is likely to be acceptable and sustainable in underserved settings. Furthermore, the findings of this study suggest that care providers view task shifting to peer health workers as possibly having the additional benefit of improving patient engagement in MTM services. However, this finding should be interpreted with caution as previous research on the role of peers in improving patient self-management, medication adherence, and patient engagement report mixed findings [93-96]. The use of peers in supporting MTM activities, therefore, needs to be investigated further to optimize MTM outcomes. Similarly, although previous research suggests that group-based care could be effective for the management of chronic diseases such as diabetes [97], the application of these approaches in the provision of MTM requires additional investigations.

There are several limitations to this study. First, by nature of being a qualitative study, the data collected may be biased by selective memory, attribution, and exaggeration of the study participants. However, the use of an online survey to verify the consistency of findings generated

by the focus group discussions could have mitigated this bias. Second, using social analysis to identify potential study participants could have biased the selection of subject since participants predominantly hailed from the pharmacy profession. Although this is reasonable given that MTM services are primarily provided by pharmacists, it is likely that the views and opinions of this group do not reflect those of other professions such as clinicians. Lastly, this study was conducted in a single organization that primarily focuses on HIV care and chronic disease management. It is possible that in different contexts, different sets of findings would be obtained.

3.5. Conclusions

Overall, this study suggests that the provision of MTM services in underserved settings could be motivated by the need to improve medication adherence, safety, and effectiveness, as well as to avert the public health risks posed by suboptimal treatment of communicable diseases. The study identifies several MTM strategies and suggests that a hybrid model involving the collaboration among professionals and lay health workers would be reasonable for providing MTM services in underserved settings. Because this study was primarily explorative, it raises a number of opportunities for future clinical and informatics research. First, further research is needed to delineate the feasibility and comparative effectiveness of different MTM approaches in order to identify the approaches that are effective, scalable, and sustainable in underserved settings. Second, the themes generated by this study could be refined further and used to inform the development of formal conceptual frameworks that would subsequently guide the implementation and evaluation of MTM services in underserved settings. Lastly, further informatics research is needed to understand how different strategies of MTM service provision in underserved settings affects the design, evaluation, and implementation of tools that support the workflows associated with these strategies.

3.6. Appendixes

Appendix 3.1: Identification of Study Participants using Social Network Analysis

Procedure

A self-report survey (Appendix 1a) was administered to a convenient sample of 45 respondents. The survey asked respondents to name the colleagues whom they consult when having patient-specific medication-related questions. The respondents also indicated the frequency of the consultations and ranked the value of advice they received from the named colleagues. The self-report survey data was extracted and used to construct a social network graph for further analysis.

Analysis

Two social network analyses were done on the constructed graph. The first analysis applied the edge betweenness community detection algorithm to discover subgraphs that represented the community whose members would be suitable focus group discussion participants. The goal of the second social network analysis was to identify key opinion leaders who would be suitable candidates for the online survey. This was achieved by computing the eigenvector centrality and betweenness centrality followed by identifying the opinion leaders as the outliers in the plot of the two metrics.

Findings

The analyzed graph had 70 nodes and 181 edges. The community detection algorithm identified 12 communities (Figure 3.2). The yellow cluster in Figure 3.2 was composed of the actors who were considered suitable targets for the focus group discussion. Seven actors from this cluster ended up participating in the focus group discussion. Figure 3.3 is the plot of eigenvector centrality versus betweenness centrality that was used to identify opinion leaders. Fifteen actors were considered opinion leaders who were suitable candidates for the online survey.

Appendix 3.1a: Social Network Analysis Survey

| | |
|--|---|
| 1. Please enter your name below | |
| | |
| 2. Briefly, describe what you do at AMPATH. | |
| | |
| 3. How long have you worked at AMPATH | |
| <input type="checkbox"/> Less than 6 months <input type="checkbox"/> 6 months to 1 year <input type="checkbox"/> 1 to 3 years <input type="checkbox"/> 3 to 5 years <input type="checkbox"/> More than 5 years | |
| 4. How long have you worked at your present job position | |
| <input type="checkbox"/> Less than 6 months <input type="checkbox"/> 6 months to 1 year <input type="checkbox"/> 1 to 3 years <input type="checkbox"/> 3 to 5 years <input type="checkbox"/> More than 5 years | |
| 5. Please name the colleagues you consult whenever you have questions about a patient's medication-related problems. (A maximum of 5 individuals can be named) | |
| Person 1 | |
| Person 2 | |
| Person 3 | |
| Person 4 | |
| Person 5 | |
| 6. How often do you contact each selected person for the advice? | |
| Person 1 | <input type="checkbox"/> Never <input type="checkbox"/> Rarely <input type="checkbox"/> Sometimes <input type="checkbox"/> Often <input type="checkbox"/> Always |
| Person 2 | <input type="checkbox"/> Never <input type="checkbox"/> Rarely <input type="checkbox"/> Sometimes <input type="checkbox"/> Often <input type="checkbox"/> Always |
| Person 3 | <input type="checkbox"/> Never <input type="checkbox"/> Rarely <input type="checkbox"/> Sometimes <input type="checkbox"/> Often <input type="checkbox"/> Always |
| Person 4 | <input type="checkbox"/> Never <input type="checkbox"/> Rarely <input type="checkbox"/> Sometimes <input type="checkbox"/> Often <input type="checkbox"/> Always |
| Person 5 | <input type="checkbox"/> Never <input type="checkbox"/> Rarely <input type="checkbox"/> Sometimes <input type="checkbox"/> Often <input type="checkbox"/> Always |
| 7. How would you rank the value of the advice you receive from each person? | |
| Person 1 | <input type="checkbox"/> Very low <input type="checkbox"/> Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> Very high |
| Person 2 | <input type="checkbox"/> Very low <input type="checkbox"/> Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> Very high |
| Person 3 | <input type="checkbox"/> Very low <input type="checkbox"/> Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> Very high |
| Person 4 | <input type="checkbox"/> Very low <input type="checkbox"/> Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> Very high |
| Person 5 | <input type="checkbox"/> Very low <input type="checkbox"/> Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> Very high |
| 8. Please use the space below for any additional comments: | |
| | |

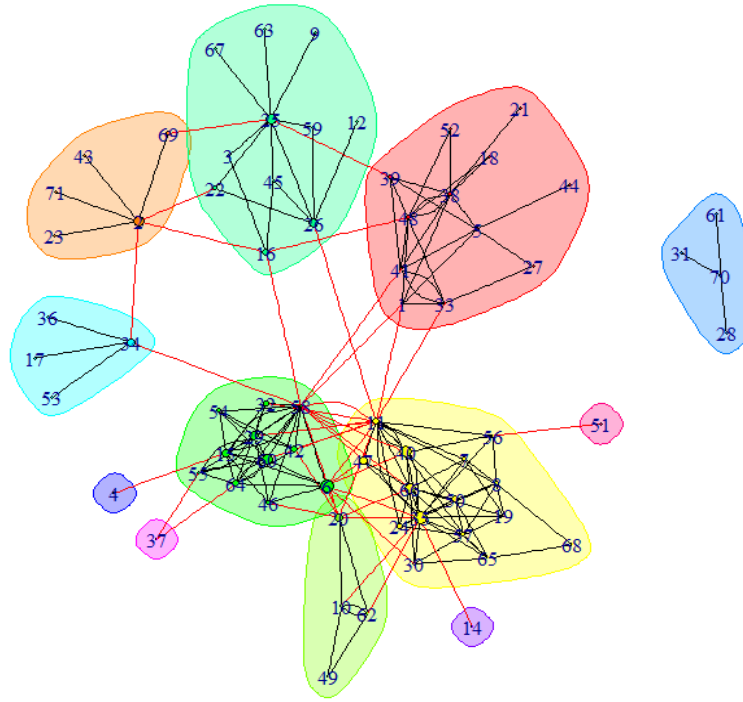


Figure 3.2: Network diagram of Communities Identified by the Edge-Betweenness Community Detection Algorithm. Nodes represent individuals, and edges indicate consultations.

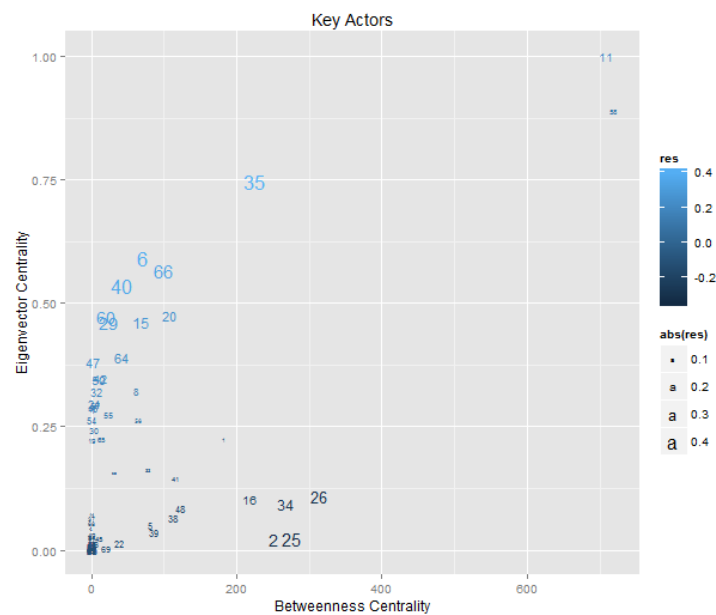


Figure 3.3: Plot of Eigenvector Centrality vs. Betweenness Centrality used to identify opinion leaders

Appendix 3.2: Focus Group Discussion Guide

1. With respect to the medication use process (Prescription, Dispensing, Administration, and Monitoring), how is care provided to ambulatory patients at AMPATH?
2. What is your opinion about the medication use process at AMPATH? What aspects are adequate? Which aspects need to be improved upon? Why? Why not?
3. What are some of the barriers and challenges of the medication use process at AMPATH?
4. Please describe how medication monitoring is currently offered at AMPATH. What are some of the ways the current approaches could be improved?
5. What patient groups would benefit from medication therapy management at AMPATH?
6. What are some of the approaches through which Medication Therapy Management Services can be offered at AMPATH?
 - a. What are the pros and cons of these approaches?
 - b. How can health information technology support these approaches??
7. Please envision the use of an information system that supports the provision of medication therapy management services. What functionalities would you desire in such a system?

Appendix 3.3: Online Survey

Medication Therapy Management Approaches

1. Please indicate your level of agreement with respect to whether the following approaches could be used to provide medication therapy management services in a resource-constrained setting:

| | Strongly Agree | Disagree | Neutral | Agree | Strongly Agree |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Professional: MTM is delivered by a trained professionals | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Group-based care: MTM is delivered to groups of patients rather than to individual patients | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Task shifting to lay health workers: MTM is primarily delivered by trained lay health workers e.g. peer health workers | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Task shifting to other professionals: MTM is delivered by other cadres of healthcare providers e.g. nurses | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Technology-centered: Most MTM activities are automated eg. Using IVR technology | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

2. Please select the top THREE approaches that you think are most useful in providing medication therapy management services in a resource-constrained setting:

- ☐ Professional approach
☐ Group-based care approach
☐ Task shifting to lay health workers
☐ Task shifting to other professionals
☐ Technology-centered approach
☐ Other: _____

3. What is the single-most-useful approach for providing medication therapy management services in a resource-constrained setting? (Please chose one)

- ☐ Professional approach
☐ Group-based care approach
☐ Task shifting to lay health workers
☐ Task shifting to other professionals
☐ Technology-centered approach
☐ Other: _____

4. Briefly, explain the reason for the choice made in the preceding question

5. Please provide any other comments you may have on the approaches that could be used to provide medication therapy services in resource-constrained setting

Medication Therapy Management Beneficiaries

6. Please indicate your level of agreement with respect to whether the following patient groups need more rigorous medication therapy management services:

| | Strongly Agree | Disagree | Neutral | Agree | Strongly Agree |
|-------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Chronic disease patients | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Geriatrics | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| HIV/TB coinfectd patients | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Newly-initiated ART patients | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Pediatrics | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Second- and third-line ART patients | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

7. Please select the top THREE patient groups that you think need more rigorous medication therapy management services:

- ☐ Chronic disease patients
- ☐ Geriatrics
- ☐ HIV/TB coinfectd patients
- ☐ Newly-initiated ART patients
- ☐ Pediatrics
- ☐ Second- and third-line ART patients
- ☐ Other: _____

8. Which single patient group would benefit the most from more rigorous medication therapy management services? (Please chose one)

- ☐ Chronic disease patients
- ☐ Geriatrics
- ☐ HIV/TB coinfectd patients
- ☐ Newly-initiated ART patients
- ☐ Pediatrics
- ☐ Second- and third-line ART patients
- ☐ Other: _____

9. Briefly, explain the reason for the choice made in the preceding question

10. Please provide any other comments you may have on patient groups you think need more rigorous medication therapy management services

Barriers and Facilitators

11. Please indicate your level of agreement with the following statements about the facilitators of the provision of medication therapy management services in a resource-limited setting:

| | Strongly Agree | Disagree | Neutral | Agree | Strongly Agree |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Evidence from previous patient-focused interventions such as the diabetes and anticoagulation clinics | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Expansions into new frontiers in chronic disease management call for more rigorous medication-related care | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Innovative approaches such as peer-based counselling and group-based care that are already being researched and are proving to be effective | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| There is a recognized requirement to conduct and support pharmacovigilance activities | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

12. Please provide any comments about the facilitators of the provision of medication therapy management services in a resource-limited setting
-

13. Please indicate your level of agreement with the following statements about the barriers to the provision of medication therapy management services in a resource-limited setting:

| | Strongly Agree | Disagree | Neutral | Agree | Strongly Agree |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Use of alternative forms of medicines by patients | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Lack of good health information technology infrastructure to support care processes | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Language barrier | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Stigma and passiveness of patients | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Inadequate knowledge and skill by care providers | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| High volumes of patients, low staffing levels, and lack of time | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

14. Please provide any comments about the barriers to the provision of medication therapy management services in a resource-limited setting
-

Goals and Priorities

15. Please indicate your level of agreement with the following statements about the goals of the provision of medication therapy management services in a resource-limited setting:

| | Strongly Agree | Disagree | Neutral | Agree | Strongly Agree |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Improve counselling, care planning, and evaluation of treatment outcomes | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Improve monitoring of medication adherence | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Improve implementation and reporting of pharmacovigilance activities | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Monitor the use of alternative forms of medicines by patients | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Improve the decision-making capacity of care providers | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

16. Please provide any comments about the goals of the provision of medication therapy management services in a resource-limited setting:

17. Please rank the following goals to reflect your thoughts on the priorities of the provision of medication therapy management services in a resource-limited setting:

| | Priority 1 | Priority 2 | Priority 3 | Priority 4 | Priority 5 |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Improve counselling, care planning, and evaluation of treatment outcomes | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Improve monitoring of medication adherence | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Improve implementation and reporting of pharmacovigilance activities | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Monitor the use of alternative forms of medicines by patients | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Improve the decision-making capacity of care providers | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

18. Please provide any comments about the priorities of the provision of medication therapy management services in a resource-limited setting:

Role of Health Information Technology

19. Please indicate your level of agreement with the following statements about the desired functions of an information system that supports the provision of medication therapy management services in a resource-limited setting:

| | Strongly Agree | Disagree | Neutral | Agree | Strongly Agree |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Patient Identification: the system should help identify patients who need additional follow-up | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Clinical Decision Support: the system should provide decision-making aids to care providers | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Communication and reporting: the system should enable effective communication and reporting | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Data Capture: The system should support efficient onsite and remote data entry | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Data Validation: the systems should support data validation through well defined checks | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Patient Data Viewing: The system should support the integrated view of relevant patient data | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

20. Please provide any comments about the role of health information technology on the provision of medication therapy management services in a resource-limited setting:

Chapter 4. Assessing ambulatory HIV care workflow patterns in underserved settings

4.1. Introduction

A *workflow* is a sequence of tasks where each task can be conceptualized as a unit of work in which *inputs* are *transformed* into *outputs* [98]. Workflows can occur between organizations, within an organization, and at an individual cognitive level and can generate, consume, or transform information [98, 99]. A *clinical workflow* is a segmental sequence of finite tasks performed during the delivery of clinical care to assess, change or maintain the health of a patient [100]. Clinical workflows are characterized by how specific clinical tasks are accomplished, the order in which the tasks are completed, the persons responsible for task completion, and the resources used to complete the task [100]. In the ambulatory care setting, an organizational-level clinical workflow may include several tasks such as appointment check-in, clinician assessment, laboratory testing, and medication dispensing.

The point-of-care monitoring of antiretroviral toxicities is an integral function of any HIV care workflow [2, 6]. Antiretroviral toxicities may range from mild side-effects to life-threatening adverse drug reactions and have been reported with the use of all antiretroviral drugs [6]. They are responsible for introducing important barriers such as medication nonadherence, treatment substitution, treatment discontinuation, and loss to follow-up that individually or collectively counteract the benefits of antiretroviral therapy [2].

The use of standardized survey tools and point-of-care clinical decision support (CDS) systems could improve the quality of antiretroviral toxicity monitoring within HIV care workflows. Compared to self-reporting by patients or open-ended questioning by care providers, screening tools such as scales, profiles, and checklists have been shown to elicit more accurate information

from patients and improve the documentation of clinical observations [24, 25]. On the other hand, point-of-care CDS interventions have been used to address information-related challenges experienced during care delivery across different settings [98]. CDS systems reduce the cognitive workload associated with care provision by facilitating the collection, analysis, and delivery of information necessary for clinical decision-making. CDS systems have been investigated by various researchers and implemented across a variety of inpatient and outpatient settings [98]. Although studies on the clinical impact of CDS report mixed findings, there is a common belief among researchers and implementers that CDS systems could be useful in improving care delivery efficiency and effectiveness [98]. In underserved care settings where skilled care providers are few, CDS applications have been used to complement task shifting of health care responsibilities from professionals to health workers with shorter training and fewer qualifications but who are more readily available [82]. Whereas the most effective targets of CDS applications in task shifting remains a research problem, researchers have developed CDS applications to facilitate different task shifting strategies such as nurse management of non-communicable diseases [82, 101] and improved range and quality of service delivered by frontline health workers [44, 102].

The design of documentation and decision-making aids for improving antiretroviral toxicity monitoring at the point-of-care requires a good understanding of HIV care workflows. Such understanding could be achieved through workflow analysis and quality improvement studies [21]. These are process redesign studies that examine current workflows, identify drivers of suboptimal performance in the current workflows, and determine how CDS tools could be designed and integrated to improve the efficiency and efficacy of the studied workflows [21]. Sheehan and Bakken state that whereas good workflow integration increases the usability, safety, and effectiveness of CDS tools, poor workflow integration may lead to care delivery disruptions,

compromised patient safety, resource underutilization, and wastage [99]. Workflow analyses are particularly important when designing CDS tools for clinical workflows in underserved settings [21]. Several factors including poor infrastructure, scarce human resources, and high disease burdens in underserved settings contributes to the uniqueness of clinical workflows in such settings and could influence the manner in which CDS tools targeting these workflows are designed.

It is plausible that antiretroviral toxicities are frequently not recognized and documented in ambulatory HIV care workflows in underserved settings because care providers lack the time and resources required for point-of-care antiretroviral toxicity monitoring. Accordingly, the purpose of the study reported in this chapter was to identify barriers to and opportunities for improving the quality of point-of-care antiretroviral toxicity monitoring in underserved settings by examining different aspects of the ambulatory HIV care workflow in an underserved setting in western Kenya.

4.2. Methods

4.2.1. Conceptual Framework

This workflow analysis study was guided by the Contextual Design framework developed by Holtzblatt and Beyer [99]. This user-centered process describes a methodology for studying workflows to inform the design of systems that address user needs [99, 103]. Contextual design involves the use of ethnographic methods such as field interviews and observations to acquire data about user workflows, and the subsequent creation of models that describe different perspectives of work. The key phases of the contextual design process are the contextual inquiry, work modeling, consolidation, and workflow redesign. These are described below.

Holtzblatt and Beyer define *contextual inquiry* as the process of understanding how people routinely conduct their work and the subsequent creation of a shared interpretation of the work [103]. The process unearths different aspects of work including the motive of the tasks, the strategy

for carrying out the tasks, the structures that enable work accomplishment, and the conceptual distinctions between different parts of work [99].

Workflow modeling refers to the creation of diagrams that describe the work of individuals and organizations based on the findings of contextual inquiries. Holtzblatt and Beyer state that workflow modeling provides system design stakeholders a language for talking about work, makes the structure of work explicit, and makes contextual inquiry data more coherent [103]. Five different models can be used to describe different perspectives of work: 1) the *flow model* illustrates how information is communicated from sources to targets in a workflow, 2) the *cultural model* illustrates how institutional culture and policy influences work, 3) the *sequence model* describes the steps needed to accomplish work, 4) the *physical model* describes the physical environment that supports work, and 5) the *artifact model* describes objects supporting the workflow such as electronic medical records and CDS tools.

Consolidation refers to synthesizing common patterns and structures of work from different contextual inquiry sources without losing individual variations [103]. Lastly, *workflow redesign* refers to reviewing consolidated data to identify ways in which technology could be integrated to improve studied workflows.

4.2.2. Study Setting

AMPATH is an umbrella healthcare organization that provides comprehensive HIV/AIDS and chronic disease care in western Kenya [77]. Although AMPATH provides care via several parent and satellite clinics scattered around western Kenya, this study was done at AMPATH's primary center in Eldoret, Kenya. At the time this study was conducted, the AMPATH Center in Eldoret served approximately 30,000 HIV patients in a catchment area with approximately 289,000 inhabitants according to the 2009 Kenya population and housing census results [104].

4.2.3. Data Collection

Contextual inquiry data was collected through individual semi-structured interviews, artifact examination, and a rapid literature review. The semi-structured interviews involved two stakeholders who were familiar with the workflow. In each interview, the respondents were asked to describe their perceptions of the HIV clinic workflow at the study setting by answering the questions: a) What does routine monitoring of antiretroviral toxicity mean to you? b) What barriers have you encountered when monitoring antiretroviral toxicity? c) How is the monitoring of antiretroviral toxicity at AMPATH carried out? The respondents were asked to give examples drawn from their individual experiences to illustrate the statements they made. They were asked follow-up questions to provide more specific details. Artifact examination involved the review of the key documents, medical records, and CDS tools used in the studied workflow.

The rapid review of literature involved reading and reviewing published literature describing the ambulatory HIV clinical workflow at the study setting. A rapid review is an accelerated synthesis of evidence from literature conducted to inform timely decision-making and to overcome time and resource limitations [105, 106]. Rapid review methodologies vary in breadth and in depth [106]. In this study, the process involved identifying publications about AMPATH by searching PubMed and extracting descriptions of the ambulatory HIV clinic workflow from the identified studies. The search strategy used was: *academic model providing access to healthcare OR AMPATH OR resource?constrained OR resource?limited AND Kenya AND (HIV?care OR HIV?treatment OR HIV?clinic*)*. The search was limited to original reports published in English between 2008 and 2017. A total of 86 records were identified and reviewed for eligibility. Studies were included if they described the flow, sequence, cultural, artifact or physical model of the ambulatory care HIV

care workflow at AMPATH. After two rounds of review, 11 studies were found to be eligible and were included in the analysis.

4.2.4. Data Analysis

Data from the semi-structured interviews were narratively reviewed, and the synthesis used to inform the initial designs of the sequence model and flow model of the studied workflow. Similarly, data from the artifact examination was narratively reviewed and used to describe the artifact model of the studied workflow.

The data from the rapid review of the literature was analyzed qualitatively using a systemic approach involving coding and identification of patterns about the intent, strategy, structure, and conceptual distinctions that constitute the ambulatory HIV care workflow at AMPATH. Articles from the rapid review of literature were uploaded to Qualitative Analysis Miner Lite [85] for software-aided coding. The goal of the coding process was to transform qualitative text excerpts into codes which could be analyzed quantitatively and subsequently used to generate patterns in data. The coding process involved the combined use of deductive codes and inductive codes [107]. Table 4.1. provides examples of coding text excerpts, codes, and code types in this study. Deductive coding involved labeling text excerpts with concepts derived from the Holtzblatt's and Beyer's Contextual Design framework [99]. For example, text excerpts describing different workflows were labeled using codes determined *a priori* such as "flow model", "physical model" and "artifact model". Inductive coding involved labeling text excerpts with codes that emerged from the reviewed text and were different from the *a priori* codes. For example, the task-related codes such as "interview patient", "review charts" and "record locator information" emerged from the reviewed data. The coding process was reiterated until saturation, after which code frequencies were computed.

Table 4.1: Examples of text excerpts, codes, and code types from the coding process

| Type | Code | Excerpt |
|-----------|----------------------------|--|
| Deductive | Physical Model | “The Eldoret clinic itself was composed of four independently functioning modules designated as 1a-1d (3 adult clinics and 1 pediatric clinic housed in a single building) for reporting purposes.” [108] |
| | Artifact model | “Clinicians caring for AMPATH patients do not enter data directly into AMRS but rather complete paper encounter forms” [14] |
| Inductive | Lack of computing Skills | “Since most clinicians in resource-limited settings are not able to use computers directly during patient-care, OpenMRS allows clinicians at AMPATH to complete data-driven, pre-printed AMPATH encounter forms (which contain coded choices) during patient visits” [109] |
| | Record Locator Information | “Trained and remunerated HIV-positive peers with records of perfect clinic and/or treatment adherence contact patients by phone or through home visits if they miss a scheduled clinic visit” [38] |

The codes generated through the coding process were used to identify themes about the intent, strategy, structure, and conceptual distinctions of the studied workflow. These constructs are defined by Holtzblatt and Beyer [110] as follows. *Intent* is the motive for accomplishing a task and is independent of the means used to achieve it. The intent of a dispensing task in a workflow is to transform a prescription order into a medication. *Strategy* is the pattern used to carry out tasks in a workflow. For example, the strategy for simple clinical workflow may consist of checking in, nurse triage, clinician encounter, dispensing encounter, and checking out in that order. *Structure* refers to the physical, organizational, or conceptual arrangements that enable the implementation of a *strategy*. To implement the strategy in the example above, the physical environment of the workflow may be structured into a check-in desk, a nursing station, a clinical assessment office, a dispensing pharmacy, and a check-out station. *Conceptual distinctions* refer to the way people think about their work and how to do it. For example, a clinician encounter task in a clinical workflow may rely on predefined concepts and terminology conduct and document observations made in the encounter.

Using the findings from the contextual inquiry, consolidated workflow models that illustrate different aspects of the studied workflow were created and described. Lastly, the strengths, weaknesses, barriers, facilitators, and process redesign recommendations for antiretroviral toxicity monitoring in the studied workflow were described.

4.3. Results

4.3.1. Code Frequencies

The coding process (conducted for the rapid literature review only) yielded 37 codes under the *actor*, *artifact*, and *task* categories. These codes were mapped from 58 sentences and paragraph text excerpts via 220 excerpt-to-code mappings. The codes *clinician* and *patient* had the heaviest weights under the *actor* category (Figure 4.1). The code *clinician* was present in 9 documents and appeared 25 out of 220 times (11.4%) in the collection. The code *patient* was present in 10 documents and accounted for 10.9% of the total code frequency in the collection. The code *data entry clerk* was the next most heavily weighted code after *clinician* and *patient* under the *actor* category. It was present in 8 documents and accounted for 4% of the total code frequency. Other codes under the *actor* category with weight >0 included *registration clerk*, *nurse*, *outreach peer*, and *pharmacy technician*.

The codes *AMRS* (AMPATH Medical Record System) and AMPATH's *paper encounter form* had the heaviest weights under the *artifact* category (Figure 4.1). These two codes were present in 10 documents in the collection, with *AMRS* accounting for 12.7% and *paper encounter form* accounting for 7.7% of the total code frequency in the collection. Other codes under the *artifact* category with weight >0 included *patient charts*, *patient summary sheet*, *AMRS decision support*, *AMRS identity card*, *AMRS summary module*, *care protocols* and *appointment card*.

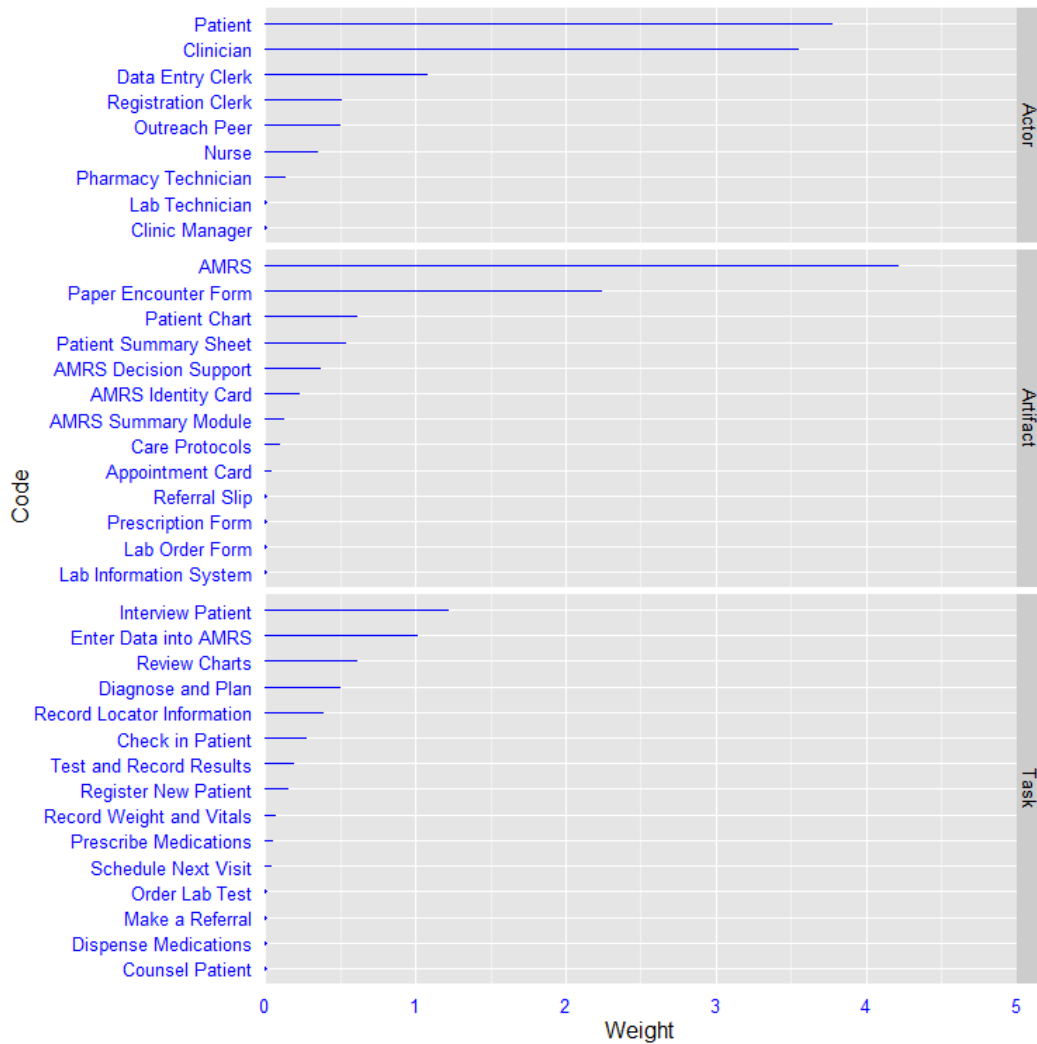


Figure 4.1: Weights of codes identified during the thematic analysis of articles describing the ambulatory HIV care workflow at AMPATH. AMRS – AMPATH Medical Record System

Under the *task* category, the most heavily weighted activities included *interview patient* (4.5% of total coding frequency, 10 documents), *enter data into AMRS* (3.6% of total coding frequency, 8 documents), *review charts* (3.6% of total coding frequency, 5 documents), and *diagnose and plan* (3% of total coding frequency, 6 documents) (Figure 4.1). Other codes in this category included *record locator information*, *check in the patient*, *test and record results*, *register a new patient*, *record weight and vitals*, *prescribe medications* and *schedule next visit*.

4.3.2. Cultural Model

AMPATH was established to provide free comprehensive HIV care to both rural and urban patients residing in western Kenya [108, 111, 112]. The organization pursues a tripartite mission of care, training, and research to address health challenges faced in underserved settings [78]. AMPATH strives to “lead with care” and provides training and mentorship to its care providers and conducts research in order to achieve this goal [78].

The cultural model of the ambulatory HIV care workflow at AMPATH demonstrates the central role of the clinician in the workflow. The clinicians in the workflow are responsible for the most influential care delivery activities including interviewing patients and recording care observations, reviewing previous patient data, diagnosing diseases and planning care, ordering laboratory tests, writing prescriptions, and scheduling patient visits. The clinicians in the workflow are primarily clinical officers (equivalent to physician assistants in the United States) who provide care with little to no supervision [14]. Consequently, the key record-keeping and decision-making aids in the workflow including the paper encounter form, the patient summary sheet, and the computer-generated care suggestions target the clinical officer cadre.

The data collected in the workflow primarily supports clinicians delivering care. The secondary uses of the collected data include program reporting to funding agencies and the government, quality improvement and research [108, 113].

4.3.3. Physical Model

The physical structure of the ambulatory HIV care workflow at AMPATH is organized into four separate ambulatory patient care modules, one clinical laboratory, and one pharmacy located in the same building. Three of the 4 patient care modules are adult HIV clinics that offer the same service, while one module is dedicated to pediatric HIV care. The patient care modules are

typically run by nurses and clinical officers. A patient is enrolled to specific care module during his/her initial encounter visit. In subsequent encounter visits, the patient receives clinical care at the module assigned to him/her. However, rather than being cared for by the same clinician at each encounter, the patient is cared for by any clinician available during the visit. Similar to the patient care modules, the AMPATH laboratory and the pharmacy are run by laboratory technicians and pharmacy technicians respectively. Patients seeking services from these locations are attended to by whichever personnel is available.

4.3.4. Artifact Model

The three main artifacts in the ambulatory HIV care workflow at AMPATH are the *AMPATH medical record system (AMRS)*, the *paper encounter forms*, and the *patient summary sheets*. The AMRS is ambulatory electronic health record (EHR) that has been used at AMPATH since 2004 to store longitudinal patient records for all AMPATH patients. It was the first implementation of OpenMRS, an open-source EHR that is widely used in developing countries [14, 114]. The patient records in AMRS consist of demographic, clinical, laboratory, and pharmacologic information stored as categorical and numeric observations of clinical concepts encoded in the AMRS concept dictionary [14, 109].

The *paper encounter forms* are used for the care of both adult and pediatric patients and include an initial visit encounter form that is filled in for new patients and a return visit encounter form that is filled for returning patient [108, 109]. These structured forms were designed with input from clinicians at AMPATH to collect a minimal data set that supports care delivery, reporting, monitoring and evaluation, and research [114]. A single form captures over 400 demographic, clinical, laboratory and pharmacologic data elements that are observed during an encounter visit and that are eventually hand-entered into AMRS [13, 108, 109, 111, 114]. The forms also contain

blank free text comment boxes that can be used by clinicians to write supplemental notes whenever necessary [109, 113]. The free text comments are matched to known concepts in the concept dictionary during data entry, with free text concepts not found in the dictionary submitted to be considered for dictionary addition [109].

The *patient summary sheets* are patient-specific reports that summarize information selected from the patient's AMRS records including identifying information, problem list, laboratory results, and medications [14, 109]. This summary report serves as a quick reference to a patient's most relevant past records and was developed to minimize the time clinicians needed to go through the patient's past encounter records [14, 109, 114]. The patient summary sheets may also contain care suggestions such as reminders to order overdue labs tests on the patient summary sheet [14, 109, 114]. They are generated as a printable pdf file by a programming module within AMRS called the *clinical summary module* [14, 109, 114].

4.3.5. Flow Model

The flow model of the ambulatory HIV care workflow at AMPATH is illustrated in Figure 4.2. This model identified the clinician as the key documenter and consumer of clinical information in the workflow. The clinician communicates directly with the patient to gather information about the patient's disease and medication status and to provide care instructions, counseling, and education to the patient. The clinician obtains additional information necessary for care delivery by reviewing the patient summary sheet or perusing the patient's paper charts, and by reviewing information such as the patient's weight and vital signs that are already recorded on the encounter form. The clinician records his/her clinical observations and care plan on the paper encounter form. He communicates indirectly to laboratory technicians and dispensing staff through lab order forms and prescriptions respectively.



Figure 4.2: Information flow model for the ambulatory HIV care workflow at the AMPATH. Nodes depict information sources and targets while arrows indicate the information that is communicated from the source to the target. Blue nodes depict human actors while green

4.3.6. Sequence Model

The ambulatory HIV care workflow at AMPATH is fairly structured. A high-level Business Process Management Notation (BPMN) 2.0 [115, 116] illustration of the sequence model of this workflow is shown in Figure 4.3. This model consists of 7 main tasks: *check-in*, *outreach*, *physical exam*, *clinician assessment*, *lab assessment*, *prescription fill* and *check-out*. A more detailed illustration of the return-visit sequence model is shown in Figure 4.4. This model shows multiple participants (represented as BPMN swim lanes) interacting to achieve the goals of the workflow.

At the start of the visit encounter, a previously registered patient presents his/her AMRS ID card to a *registration clerk*. The clerk starts the clinic process by checking in the patient and entering the patient's identifier information on a new *encounter form*. Next, the patient is directed to AMPATH's outreach program where a trained *outreach peer* health worker collects the patient's up to date locator information including cell phone numbers, physical addresses, and nearest landmarks to physical addresses. Once the outreach information is collected, the patient is directed to a nursing station. Here, a *nurse* examines the patient and records the patient's weight and vital signs on the paper encounter form. After the nurse assessment, the patient waits to be seen by a clinician for clinical assessment. In the clinical encounter, a *clinician* interviews the patient and records observations about the patient's disease status (e.g., chief complaint, signs, symptoms, and physical findings) and the patient's medication status (e.g., current medications, adherence, and toxicities). The clinician also records the diagnosis and the care plan he/she has come up with on the paper encounter form. To help clinicians with decision-making during care planning, a summary report of the patient's previous encounters is made available to the clinician. These summary reports are created by a CDS module with AMRS that extracts structured information from pre-defined data in the AMRS. The reports may contain care suggestions and reminders.

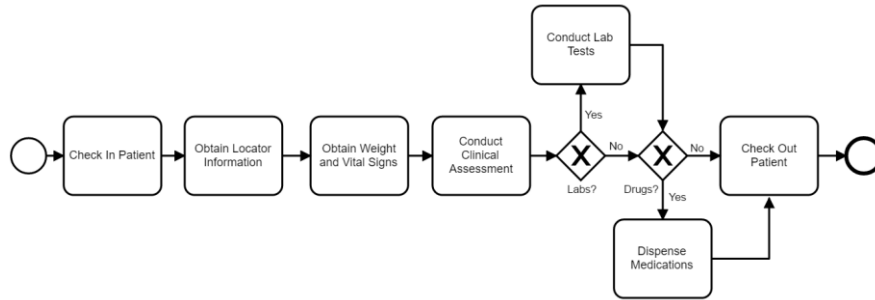


Figure 4.3: A high-level BPMN 2.0 illustration of the sequence of tasks in the ambulatory HIV care workflow at AMPATH

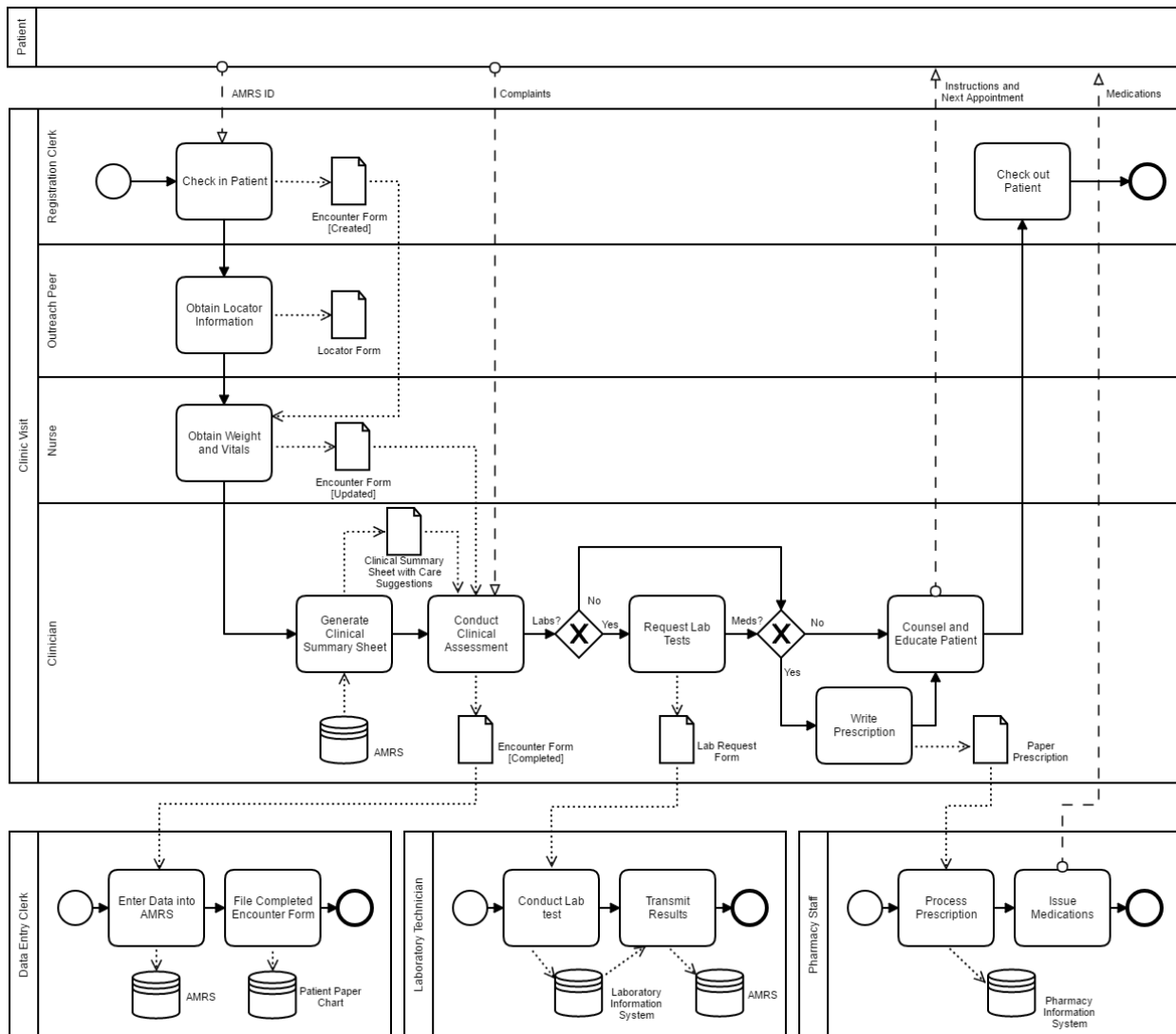


Figure 4.4: A high-level descriptive BPMN 2.0 illustration of the return-visit ambulatory HIV care workflow at AMPATH. AMRS – AMPATH Medical Record System.

As part of the care plan, the clinician may order laboratory tests, medications, or both. If the clinician orders tests, he/she fills a paper laboratory requisition form and hands it over to the patient. The patient goes to the AMPATH laboratory and hands over the requisition form to a laboratory technician. The technician collects samples from the patient and conducts the ordered laboratory tests. The technician enters the results into the department's laboratory information system. These results are then transmitted to the AMRS and are made available in the subsequent visits as part of the patient's summary report. If the clinician orders medications, he writes a paper prescription and hands it over to the patient who goes to the pharmacy where the prescription is filled. Patients waiting for their medications to be dispensed may be counseled and educated by trained peer health workers albeit informally. If the clinician orders laboratory tests and prescribes medications in the same encounter, the patient is instructed to go the laboratory before going to the pharmacy. The clinic encounter is completed when the patient leaves the clinic. After the clinic visit, data entry clerks retrospectively enter the encounter data from completed paper encounter forms into the AMRS. To validate the quality of the data entry process, quality management clerks review a random 10% of the paper encounter forms for data entry errors.

4.3.7. Strengths, Weaknesses, Barriers, and Facilitators

Table 4.2 summarizes the key strengths, weaknesses, barriers, and facilitators pertaining to the point-of-care monitoring of antiretroviral toxicity identified from the analysis of the ambulatory HIV care workflow at AMPATH. These factors primarily pertain to the documentation and analysis of antiretroviral toxicities and were synthesized from information from the different workflow models identified in this study. They are described in more detail below.

Table 4.2: Summary of the key strengths, weaknesses, barriers, and facilitators of antiretroviral toxicity monitoring identified from the workflow analysis

| Category | Description |
|--------------|--|
| Strengths | <ul style="list-style-type: none"> • Adequate documentation of patient-reportable medications • Adequate documentation of clinician-instituted medication plans • Reasonable assessment of medication adherence • Comprehensive documentation of physical exam findings |
| Weaknesses | <ul style="list-style-type: none"> • Inadequate documentation of patient-reportable symptoms and risk factors • Inadequate documentation of clinician-identified medication toxicities • Lack of documentation of clinician reasoning about medication toxicities |
| Barriers | <ul style="list-style-type: none"> • Clinician time and workload constraints • Data collection form design limitations • Institutional policies on documentation |
| Facilitators | <ul style="list-style-type: none"> • Opportunities for delegating tasks to available lay health workers • Potential to use clinic wait times for additional data collection • Availability of structured data in electronic health records • Clinician experience with electronic health records and clinical decision support |

Strengths

Collectively, the information on patient-reported medications, clinician-ordered medications and medication adherence are important in establishing the causality of antiretroviral toxicities. One of the key strengths of the AMPATH workflow is the documentation of medications commonly prescribed in the workflow. This is done in the *current medications* section of the encounter form. The clinician documents patient-reported medications by checking off lists that describe medications used for HIV treatment, *Pneumocystis jiroveci* pneumonia prophylaxis, cryptococcal meningitis treatment, tuberculosis prophylaxis, and tuberculosis treatment. The clinician can also document additional medications reported by the patient on a free text ‘other medications’ field under this section. A similar approach is used to document the medications prescribed by the clinician under the *care plan* section of the encounter form.

In addition to the documentation of medications prescribed, the encounter form reasonably captures medication adherence. This is subjectively assessed using patient self-reporting and recorded as good, fair, or poor under the adherence section of the encounter form. The reasons for non-adherence is captured by checking off a list of potential reasons that contains descriptions such as ‘forgot’, ‘felt better’, ‘Lost/ran out of pills’ and ‘Pill burden’. Another strength of the AMPATH workflow is the comprehensive documentation of physical examination findings. This information could be used to determine manifestations and patterns of antiretroviral toxicities experienced by individual patients.

Weaknesses

A key weakness of the workflow is the inadequate documentation and interpretation of patient-reportable symptoms. This is exemplified by the fact there is no dedicated section of the encounter form that adequately captures patient-reported symptoms. The only patient-reportable symptoms encoded in the AMPATH’s adult return-visit HIV encounter form pertain to the monitoring of tuberculosis (12 symptoms) and the risk of HIV transmission (3 symptoms). These symptoms overlap with only 5 (25%) of the symptoms in the widely-adopted and validated 20-item HIV Symptom Index [117].

Another weakness of the workflow is that clinician-identifiable toxicities are restricted to few treatment-limiting adverse drug reactions. The *drug side effects/toxicity* section of the encounter form allows clinicians to record their judgments on whether a patient experienced an antiretroviral toxicity, the drug responsible for the toxicity, the severity of the reaction, the clinician-identified symptoms associated with the reaction, and the level of certainty that the drug caused the identified symptoms. However, only 9 of the 24 major antiretroviral toxicities described in the World Health Organization clinical guidelines for Antiretroviral Therapy [2] are coded in the encounter form.

Although it is possible for clinicians to record additional antiretroviral toxicity observations through free text fields on the encounter form, the types and completeness of the antiretroviral toxicity observations reported using this approach were not discernable in this study.

Additionally, the reasoning behind clinical decision-making is not captured on the encounter form adequately. For example, clinicians can record the antiretroviral toxicities that they have identified based on their clinical judgments. However, the relationships between the identified antiretroviral toxicities and other observations such as signs and symptoms that are recorded are not explicit. This limits the secondary use of the data collected in the workflow as it is nontrivial to ascertain how clinicians make inferences from encounter data.

Barriers

The main barriers to the antiretroviral toxicity documentation and analysis pertain to clinician time and workload constraints. Clinicians are already expected to go through more than 400 observable entities on the encounter form during a single encounter with a patient. It may, therefore, be very challenging for clinicians to take up the additional documentation tasks required for rigorous antiretroviral toxicity monitoring.

Another key barrier pertains to inadequacies in the design of the encounter forms used in the workflow. As alluded to earlier, the encounter forms do not adequately capture information on symptoms and risk factors. Additionally, the design of the forms does not allow easy tracking of clinician reasoning, making the reuse of the collected data more difficult. Furthermore, possible barriers associated with institutional policies and goals could be identified. For example, although the content and design of the AMPATH encounter form are determined by clinicians, they are also influenced by the need to adhere to requirements set forth by the government and funding agencies. This also implies that redesigning existing encounter forms to improve toxicity monitoring is

nontrivial and would require consensus among multiple stakeholders. Furthermore, if new forms are designed for collecting antiretroviral toxicity data, then new barriers such as the need to adapt to the use of new forms, workflow reorganization, and overhead costs arise.

Facilitators

Several facilitators of antiretroviral toxicity monitoring in the studied workflow exist. One such facilitator is the ability to shift data collection tasks from the overstretched clinicians to more readily available health workers. The observation that peer health workers support the collection of outreach contact and locator information in the ambulatory HIV care workflow at AMPATH demonstrates that task shifting strategies are considered acceptable and can be successfully incorporated into HIV workflows in underserved settings. Similar strategies could, therefore, be used to enhance antiretroviral toxicity data collection during clinic visits. Additionally, the availability of ample clinic wait times which account for most of the time spent by the patient in the clinic [21, 113] could facilitate data collection through task delegation.

The availability of structured, longitudinal EHR data also presents a valuable opportunity for improving antiretroviral toxicity management. The information collected in several sections of AMPATH's encounter form and subsequently stored in the AMRS could be used to support automated inferences about antiretroviral toxicities. The fact that clinicians in the workflow already have experience using EHRs and CDS also presents a valuable opportunity with respect to the development of solutions that rely on similar approaches. For example, adopting and designing antiretroviral toxicity reports in a manner similar to the patient summary sheets currently used at AMPATH would improve their usability and learnability as clinicians are already familiar with the approach.

4.3.8. Process Redesign and Quality Improvement Considerations

Several quality improvement approaches could be considered to enhance antiretroviral toxicity monitoring in the ambulatory care workflow at AMPATH. These have been summarized using the Clinical Decision Support/Quality Improvement (CDS/QI) worksheet illustrated in Table 4.3. In line with the barriers and facilitators discussed in the previous section, the most relevant workflow redesign recommendations for improving the quality of antiretroviral toxicity monitoring in the studied workflow pertain to enhancing the collection and analysis of antiretroviral toxicity data. Figure 4.5 uses a redesigned sequence model of the ambulatory HIV care workflow AMPATH to illustrate how such quality enhancements could be achieved.

The collection of patient-reported antiretroviral toxicity data could be enhanced by incorporating more readily-available healthcare personnel into the clinical workflow. For example, peer health workers could take up data collection responsibilities as described in Table 4.3 and illustrated in Figure 4.5. This task redistribution approach could be standardized by using computer-generated survey tools such as checklists whose contents are based on clinical practice guidelines. The additional antiretroviral toxicity data collected from the patient could then be presented to the clinician to guide further antiretroviral toxicity assessments and decision-making.

Concurrently, longitudinal EHR data could be analyzed to detect possible antiretroviral toxicities in individual patients. The results of such analyses could be made available to clinicians as antiretroviral toxicity reports as illustrated in Figure 4.5. Such an endeavor is supported by the fact that the clinicians in the ambulatory HIV workflow at AMPATH are already accustomed to using clinical summary sheets that may also contain care suggestions [13, 14, 61]. It is, therefore, plausible to expect that adopting a similar strategy would enhance the uptake and ease of use of antiretroviral toxicity summary reports in the workflow.

Table 4.3: CDS/QI worksheet for Improving Antiretroviral Toxicity Monitoring in the Ambulatory HIV Workflow at AMPATH

| | Not Visit Related | Before Patient Comes to Office | Check-in and Waiting | Clinical Provider Encounter | Pharmacy Encounter | After Patient Leaves Clinic |
|---------------------------------|---|---|---|---|---|--|
| Current Information Flow | The pursuit of opportunities for finding, linking, treating & retaining HIV patients. | <p>Clinical visits are scheduled.</p> <p>Patients missing appointments tracked by the outreach department</p> | Nurse records patient body weight and vital signs | <p>Clinician use structured encounter forms to document care</p> <p>Summary sheets of previous patient data available</p> <p>Care suggestions and reminders (e.g. order overdue labs) provided on summary sheets</p> | <p>Peer health workers provide informal group counseling and education as patients wait</p> <p>Pharmacy staff dispense medication and counsel patients on medication administration</p> | Retrospective data entry of encounter information |
| Potential Enhancements | Consider opportunities for home-based tracking of disease and medication experiences | Improve pre-visit planning by sending reminders and visit plans to patients. | Have peer health workers collect patient-reported antiretroviral toxicity data using standard forms | <p>Have clinicians review antiretroviral toxicity data collected by the peer health workers</p> <p>Provide antiretroviral toxicity summary reports to clinicians</p> <p>Provide care suggestions for possible antiretroviral toxicities</p> | <p>Provide additional training materials and visual aids for peer health workers</p> <p>Provide regimen-specific dispensing information to patients</p> | <p>Consider opportunities to review the patient's care plan and medications before he/she leaves the clinic.</p> <p>Provide structures that enable recalling patients when mistakes are identified</p> |

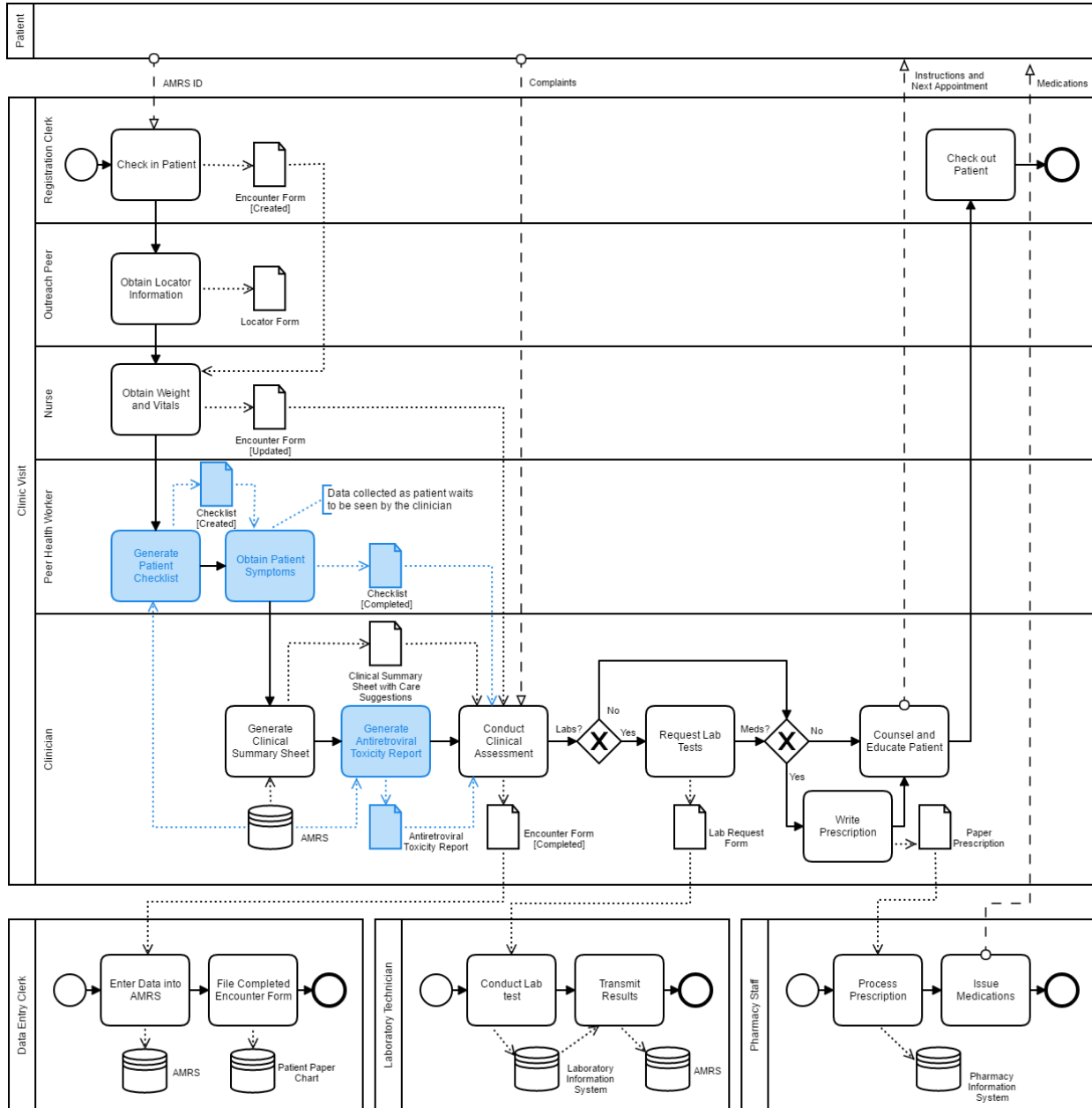


Figure 4.5: A high-level descriptive BPMN 2.0 illustration of a redesigned return-visit ambulatory HIV care workflow at AMPATH. Enhancements are color-coded in blue and show how toxicity data collection and analysis could be enhanced. AMRS – AMPATH Medical Record System

4.4. Discussion

The findings of this study suggest that ambulatory HIV care workflows in underserved settings are primarily designed to document care observations using structured encounter forms. Accordingly,

barriers to the recognition of antiretroviral toxicities in the workflow were pinpointed to the documentation and interpretation of patient-reportable and clinician-identifiable antiretroviral toxicity observations. This suggests that efforts should be directed towards improving the point-of-care processes associated with the collection, analysis, and decision-making of antiretroviral toxicity data, possibly through the combined use of task-redistribution and guideline-based clinical decision support (CDS).

The flow and sequence models described in this study corroborated the findings from previous studies that identified clinicians, particularly clinical officers (same as physician assistants in the United States), as the integral personnel in ambulatory HIV care workflows in underserved settings [21, 118]. This study also confirmed that the information generated by the ambulatory HIV care workflow is primarily consumed by the clinicians to support care planning activities such as prescribing medications, ordering laboratory tests and referring patients to other care providers [114]. These observations suggest that the application of CDS tools to enhance the quality of point-of-care antiretroviral toxicity monitoring in underserved settings should target clinicians as the primary users. Furthermore, the content and functionality of such CDS tools should be tailored to the level of skills and knowledge of clinical officers (equivalent to physician assistants in the United States) who routinely provide HIV care in underserved settings.

The observation that clinicians were the primary collectors of care information in the ambulatory HIV care workflow in underserved settings has important implications for enhancing point-of-care antiretroviral toxicity monitoring. The findings of this study suggest that clinicians in underserved settings bear the most burden of associated with the documentation of clinical observations. Such documentation is expected to be completed within a limited amount of time available to perform clinical duties as demonstrated by the time in motion study by Were et al. [21]. At the same time,

a considerable portion of the clinician's time is spent on tasks that do not require specialized skills [21]. These observations mutually suggest that it is not desirable to have clinicians collect antiretroviral toxicity information data at the point-of-care and that redistributing these tasks to less-skilled but more readily available care providers could be more meaningful. Additionally, the studies by Were et al. [21] and Tierney et al. [113] demonstrate that patients in ambulatory HIV care workflows in underserved settings spend a considerable amount of time waiting to be seen by clinicians. This presents a valuable opportunity for collecting patient-reportable antiretroviral toxicity data, with the collected information subsequently used by the clinician during care delivery.

This study had some important limitations. First, because the study analyzed the workflow in a single setting, the results may not be generalizable to other settings. Second, due to time and resource constraints, ethnographic data collection was limited to interviews with two conveniently-selected stakeholders. This could have limited the variety of responses obtainable from interviews and could have made it difficult to ascertain the true state of the studied workflow. Nonetheless, supplementing the ethnographic approach with the rapid review of the literature reporting research conducted in the studied setting was used to triangulate and clarify the findings of the ethnographic interviews. However, using the rapid review process means relying on information that could be outdated to describe the workflows that evolve with time.

4.5. Conclusions

Overall, this study suggests that the barriers to point-of-care monitoring of antiretroviral toxicities within ambulatory HIV care workflows in underserved settings could be pinpointed to processes involving the documentation and analysis of patient-reportable and clinician-identifiable antiretroviral toxicity data. This research also demonstrates that opportunities for improving the

quality of point-of-care antiretroviral toxicity monitoring in underserved settings exist in the form of redistributing antiretroviral toxicity data collection tasks from clinicians to more readily available care providers, and capitalizing on patient clinic wait times to collect the data necessary for antiretroviral toxicity monitoring. Furthermore, opportunities exist for incorporating CDS tools that analyze patient-specific antiretroviral toxicity data and provide guideline-based recommendations that support clinician decision-making pertaining to antiretroviral toxicity monitoring. Future clinical research should explore the barriers and facilitators that are intrinsic to human actors in the studied workflow. Further clinical research is also needed to investigate the role of peer health workers in collecting patient-reportable antiretroviral toxicity symptoms. Future informatics research should explore the use of documentation and decision-aids to support the collection of antiretroviral toxicity data by lay health workers, and decision-making by clinicians. Additionally, since this study did not focus on workflow efficiency, future informatics research such as time-motion studies are needed to understand the time taken to complete each task in the studied workflow.

Chapter 5. Development of a knowledge-based application prototype implementing clinical guidelines for point-of-care antiretroviral toxicity monitoring

5.1. Introduction

The World Health Organization (WHO) recognizes the need to improve the monitoring of antiretroviral toxicity [2]. It places particular emphasis on underserved settings where the range and patterns of antiretroviral toxicities may alter the need for and frequency of antiretroviral toxicity monitoring [10]. The WHO recommends a symptom-directed antiretroviral monitoring approach where clinicians assess signs and symptoms reported by patients and subsequently draw conclusions about antiretroviral toxicities [2, 22]. However, the labor intensity associated with data gathering and analysis using the symptom-directed approach limits its utility in underserved settings which face health workforce challenges [11, 12]. Consequently, it is essential to develop strategies that improve the quality of the symptom-directed antiretroviral toxicity monitoring in underserved settings by facilitating documentation and decision-making. Empirical research evidence from underserved settings shows that the use of electronic point-of-care clinical decision support (CDS) tools in the clinical management of HIV improves adherence to HIV clinical guidelines and makes the collection, analysis, and interpretation of clinical data easier [14, 15]. However, there is little evidence to demonstrate how such tools could be applied to improve symptom-directed monitoring of medication safety within HIV care workflows. Furthermore, research in the development and application of standard definitions, formatting, and reporting associated with symptom-directed monitoring of antiretroviral toxicity is limited.

A potentially useful approach to improving the quality of point-of-care antiretroviral toxicity monitoring in underserved settings is the adoption of knowledge-based CDS systems. The term ‘knowledge base’ originates from the field of artificial intelligence and refers to a repository of

facts, heuristics, and models that represent domain knowledge that can be used for problem-solving and analysis of organized data [119]. Knowledge bases are distinct from databases as the latter are collections of individual observations without any problem solving or analytic functionality [119]. Unlike mathematical or statistical approaches that use numerical representation and arithmetic manipulation to quantitatively model relationships that support inferences in a given domain, knowledge-based approaches rely on symbolic manipulations that use ontologies and apply logic to draw conclusions from asserted facts [120, 121].

A knowledge-based system is a software application that uses the knowledge stored in its knowledge base to analyze problems and provide advice within a restricted domain and like human domain experts [121]. Knowledge-based systems are primarily developed and used to increase the reproducibility, scalability, and accessibility to complex reasoning and decision-making tasks [122]. Within the biomedical domain, a good example of a foundational knowledge-based system is the MYCIN system. This rule-based computer-assisted decision support system was developed in 1976 by Ted Shortliffe et al. to support inference on the selection of antibiotic therapy for patients with bacterial infections [121, 123]. Currently, knowledge-based systems are applied in several biomedical domains including but not limited to clinical decision support systems, surveillance in public health datasets, and hypothesis generation in large-scale research datasets [122].

The purpose of this chapter is to describe the construction of a knowledge-based application prototype that implements clinical practice guidelines for antiretroviral toxicity monitoring and that is intended to support the symptom-directed antiretroviral toxicity monitoring within HIV care workflows. This chapter presents an overview of the motivation for building the prototype,

describes the development process, and discusses the challenges in the design and construction of the prototype.

5.2. Methods

5.2.1. Problem Identification and Motivation

The need for improved antiretroviral toxicity monitoring in underserved settings motivated the development of the prototype described in this chapter. Based on the studies described in Chapters 3 and 4, the barriers to antiretroviral toxicity monitoring in underserved settings were pinpointed to processes involving documentation and interpretation of antiretroviral toxicity at the point of care. In brief, the key barriers include clinician time and workload constraints, limitations in the design of data collection forms, and the failure to capture the reasoning behind clinician decision-making adequately. At the same time, the studies in Chapters 3 and 4 identified several opportunities to improve antiretroviral toxicity monitoring. These include the availability and acceptability of the use of lay health workers who could be trained to take up data collection duties, ample clinic wait times that could be used to collect additional patient-reported data, and the availability of electronic health record (EHR) data that could be analyzed for informed decision-making. Accordingly, the construction of the knowledge-based application prototype described in this chapter was motivated by the desire to address the workflow barriers and capitalize on the opportunities described above.

5.2.2. Development Objectives

The objective of the development was to construct a knowledge-based application prototype that facilitates the documentation and analysis of antiretroviral toxicity data within ambulatory HIV care workflows. The prototype generates toxicity summary reports that describe possible antiretroviral toxicities detected from patient-specific EHR data. It also generates customized

checklists that can be used to collect patient-reportable data and to identify possible antiretroviral toxicities experienced by individual patients. Similar to a diagnostic decision support system [124], clinicians can use both outputs of the prototype to confirm or rule out antiretroviral toxicities experienced by individual patients, and if necessary conduct additional assessments to narrow down diagnoses. These functionalities are described further below.

a) Detection of antiretroviral toxicities and risk factors from structured EHR data

The prototype generates summary reports describing possible antiretroviral toxicities and risk factors of antiretroviral toxicities identified from structured EHR data. The detection of antiretroviral toxicities by the prototype is based on the “Possible” causal category of the WHO-UMC (World Health Organization-Uppsala Monitoring Center) system for standardized causality assessment [125]. The assessment criteria for this category requires the ascertainment of reasonable temporal association between medication administration and the occurrence of a toxicity. Therefore, causality by other medications or disease states cannot be ruled out.

The prototype detects possible antiretroviral toxicities in EHR data via several steps as follows. First, the prototype queries longitudinal EHR data to select the list of medications that constitute the patient’s active antiretroviral regimen and the dates when each drug was first prescribed. Next, the prototype queries the longitudinal EHR data to select the clinical observations (signs, symptoms, clinical findings and laboratory findings) recorded in the EHR. Subsequently, for each pair of antiretroviral drug and clinical observation, the prototype computes the difference between the date when the clinical observation was recorded and the date when the antiretroviral drug was ordered. It then compares the date differences to predetermined time frames and selects the observations having reasonable temporal relationships to medication orders. Lastly, the prototype matches the lists of selected medications and observations with the antiretroviral toxicity concept-

concept relationships in its knowledge base to generate a list of possible antiretroviral toxicities as output. Accordingly, if the medication *abacavir* with the recording date *2017-01-14* is identified as active, and the observation *rash* with recording date *2017-01-25* is found in the EHR, then the prototype generates the output *abacavir hypersensitivity* since *rash* is a manifestation of hypersensitivity due to abacavir.

The detection of possible risk factors proceeds similarly. However, some risk factor observations do not require temporal association with the administration of medications. For such risk factors, the prototype select lists of active medications and the list of observations (regardless of the dates when they were recorded) and matches these to the antiretroviral toxicity risk factor knowledge in its knowledge base. For example, if the medication *nevirapine* is identified as active and the observation *female gender* is also identified, then the prototype generates the output *female gender is a risk factor of nevirapine hepatotoxicity*.

Both outputs of the antiretroviral toxicity and toxicity risk factor detection are provided in the same summary report generated by the prototype. These reports are intended to assist professional clinicians conducting a symptom-directed assessment of antiretroviral toxicities within ambulatory HIV workflows.

b) Generation of checklists for documenting antiretroviral toxicity

The prototype generates checklists for documenting patient-reportable symptoms of antiretroviral toxicity. The contents of the checklists are tailored to the antiretroviral regimen in a patient's current medication list. Accordingly, two patients on different treatment regimens would use different checklists. To generate a checklist, the prototype queries the patient's longitudinal EHR data to select all antiretroviral medications in the patient's current medication list. Next, it queries its knowledge base to select a list of ingredient-toxicity-toxicity observation triples that match the

previously identified antiretroviral toxicities. Accordingly, If *abacavir* was selected from the patient's medication list, examples of triples selected from the knowledge base include *abacavir-hypersensitivity-fever*, *abacavir-hypersensitivity-rash*, and *abacavir-hypersensitivity-fatigue*. This output is used to generate a checklist of symptoms matched to possible antiretroviral toxicities through many-to-many mappings.

The checklists generated by the prototype are designed for use by lay health workers to collect data about the symptoms associated with possible antiretroviral toxicities during routine clinic visits. The collected data could then be used by clinicians to confirm or rule out possible antiretroviral toxicities or to guide further clinical evaluation of the patient.

c) Additional functionalities

The prototype has *observation checker* which enables the user to match symptoms and antiretroviral drugs to identify possible antiretroviral toxicities. The prototype also serves as a repository for general browsing of information about antiretroviral regimens including their constituents. This repository provides information about specific antiretroviral drug interactions and adverse reactions, as well as the guideline-based recommendations for their management.

5.2.3. Development Process

The overall goal of the development was to create a stable and functional knowledge-based application prototype that meets the objectives described in the previous section. The development of the prototype followed the knowledge engineering cycle [122]. The key components of this process include knowledge acquisition, knowledge representation, system implementation, and system verification and validation [122]. Figure 5.1 illustrates knowledge engineering steps applied during the development of the prototype. These steps are described further below.

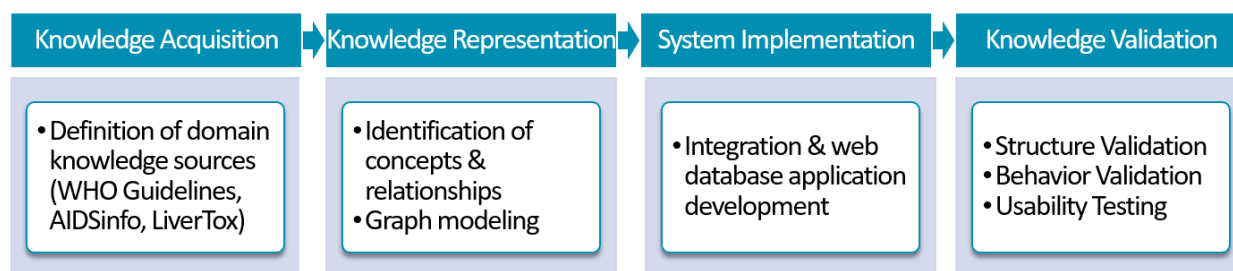


Figure 5.1: Illustration of the knowledge engineering process used to develop and evaluate the knowledge-based application prototype used in the dissertation

a) Knowledge Acquisition

Knowledge acquisition refers to the process of eliciting information from domain expert knowledge to create electronic knowledge bases [121]. Three key data sources from which the knowledge content of the prototype was derived were identified during knowledge acquisition. The WHO clinical practice guidelines on the use of antiretroviral drugs [2] was identified as the primary source of information about the key antiretroviral drugs, antiretroviral drug regimens, major antiretroviral toxicities, risk factors, and suggested management of antiretroviral toxicities. AIDSinfo, a United States government service that provides up-to-date information on federally approved HIV/AIDS medical practice guidelines and HIV/AIDS-related drugs [126] was identified as the primary reference for approved drug label information. It was used to provide knowledge about the clinical observations (signs, symptoms, clinical findings and laboratory findings) as well as their temporal associations with specific antiretroviral toxicities. Lastly, the United States National Library of Medicine (NLM) LiverTox[®] website [127] was identified as a resource for characterizing drug-induced liver injury. Information from the three data sources was primarily available in the form of unstructured and unannotated textual narratives. Table 5.1 illustrates information from the three data sources using *nevirapine hepatotoxicity* as an example. All the acquired information was manually analyzed and used to create a specification from which the knowledge-based application prototype was designed.

Table 5.1: Example of information in data sources illustrated using nevirapine hepatotoxicity

| Source | Category | Example |
|--------------------------|--|--|
| WHO Guidelines | Antiretroviral drug | Nevirapine |
| | Regimen | Tenofovir Disoproxil + Lamivudine + Nevirapine |
| | Major types of toxicity | Hepatotoxicity |
| | Risk factors | High baseline CD4 cell count (CD4 count >250 cells/mm ³ in women or >400 cells/mm ³ in men) |
| | Suggested Management | If hepatotoxicity is mild, consider substitution with Efavirenz including in children 3 years and older. |
| Product Label (AIDSinfo) | Clinical Observations | The risk of symptomatic hepatic events regardless of severity is greatest in the first 6 weeks of therapy. The risk continued to be greater in the nevirapine groups in controlled clinical trials through 18 weeks of treatment. However, hepatic events may occur at any time during treatment. In some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately half of the patients with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. |
| LiverTox® | Clinical Observations (Hepatic manifestations) | Therapy with nevirapine is associated with significant elevations in ALT levels (above 5 times the upper limit of normal) in 4% to 20% of patients and symptomatic elevations in 1% to 5% of patients. These elevations are usually transient but can be symptomatic and may require discontinuation of nevirapine. |

b) Knowledge Representation

Knowledge representation refers to the use of symbols to denote external facts in a form that facilitates reasoning and decision-making by an intelligent being or computer. According to Davis et al., a knowledge representation serves five key roles: a) It is a surrogate that supports inference through reasoning about things rather than by taking action upon them, b) It is a set of ontological commitments that determines what and how the world is perceived, c) It is a fragmentary theory of intelligent reasoning comprised of three components including the representation's conception of intelligent reasoning, the set of inferences it sanctions, and the set of inferences it recommends,

d) It serves as a medium for pragmatic, efficient computation, and e) It serves as a medium of human expression that provides a language in which people can communicate about things [128].

The goal of the knowledge representation in the development of the prototype was to identify relevant entities and relationships from the data sources described in the knowledge acquisition step and to subsequently create a model that captures the semantics of the content of the data sources. The purpose of creating the model was to support reasoning about possible antiretroviral toxicities and their manifestations that could be inferred from both individual antiretroviral drugs and regimens (combinations of individual drugs). The knowledge representation task proceeded manually and iteratively. Concepts and relationships were identified from the knowledge resources selected for the development process. The information was modeled in a labeled property graph in which the concepts are represented as vertices (nodes), binary relationships between concepts are represented as edges, and labels represented concept categories. The labeled property graph was selected as the knowledge representation formalism as it provides an intuitive and easy to understand approach for modeling highly connected information [129].

c) Knowledge-based System Implementation

The graph model was implemented in a knowledge base stored in a MySQL database. The content of this knowledge base was derived from the data sources identified during knowledge acquisition. Ingredients, multiple ingredients, and clinical drugs concepts and their relationships were described using RxNorm terms and codes [130]. Toxicities and the observations associated with toxicities were described using MedDRA (Medical Dictionary for Regulatory Activities) terms and codes [131]. Since both RxNorm and MedDRA are source vocabularies in the Unified Medical Language System (UMLS) [132], Concept Unique Identifiers (CUIs) and Atomic Unique Identifiers (AUIs) from the UMLS were also used to describe concepts in the prototype's

knowledge base. Concepts and relationships that were not found in standard vocabularies were manually curated and incorporated into the prototype's knowledge base.

The knowledge-based application prototype was designed to be compatible with OpenMRS, an open-source medical record system that is widely used in underserved settings [64]. OpenMRS stores demographic, clinical, laboratory, and pharmacologic information as structured (coded) observations of concepts from a formal concept dictionary [133]. This dictionary is centrally maintained by the Columbia International eHealth Laboratory (CIEL) and maps concepts in OpenMRS to standard terminologies including SNOMED-CT (Systematized Nomenclature of Medicine – Clinical Terms) and RxNorm [133, 134]. To enable compatibility with OpenMRS, one-to-one mappings between the concepts in the prototype's knowledge base and the concepts in the CIEL dictionary were identified and incorporated into the knowledge base. This was achieved by converting the UMLS CUIs in the prototype's knowledge base to SNOMED-CT and RxNorm codes using relationships present in the UMLS, and subsequently converting these to CIEL codes using relationships present in OpenMRS. String-matching and manual comparisons were attempted for concepts that could not be mapped automatically using unique identifiers. Additional rule tables and queries were created to map CIEL concepts with categorical or numeric data types to single concepts in the prototype's knowledge base. Accordingly, an observation in OpenMRS of the CIEL concept *serum glucose* having a numeric value less than 4 mmol/L is mapped to the MedDRA concept *blood glucose decreased* in the knowledge base.

The prototype was implemented as a two-tier web database application. The web application interface of the prototype runs on a Java Client, while its knowledge base and inference engine run on a MySQL server. A visual illustration of this architecture is shown in Figure 5.2.

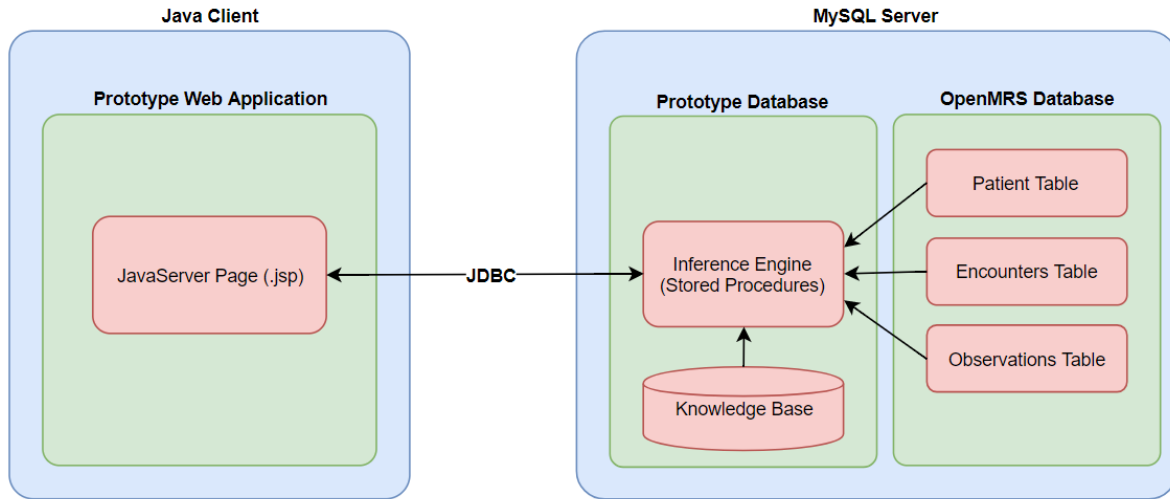


Figure 5.2: Two-tier web database application architecture of the knowledge-based prototype

The web application employs a variety of technologies including JavaServer Pages (JSP), JSP Standard Tag Library (JSTL), JavaScript, HTML5, and Cascading Style Sheets (CSS). It communicates directly with the prototype's MySQL database via the Java Database Connectivity (JDBC) Application Programming Interface (API) to enable user interaction with the prototype. Reasoning in the knowledge-based application prototype is achieved by ontology query. Ontology querying involves applications traversing the relationships linking individual entities in an ontology to answer questions about the entities' relationships [120]. For example, to identify possible antiretroviral toxicities and toxicity risk factors of a given patient, the prototype queries the OpenMRS database and selects data from different tables in OpenMRS. For example, demographic information (e.g. age, and gender) is selected from the *patient table*, while encounter ids and encounter dates are selected from the *encounter table*. Clinical observations are selected from the *observation table*. Using the selected information, the query traverses relationships in its rule engine and knowledge base to arrive at the relevant conclusions about possible antiretroviral toxicities and risk factors.

d) Knowledge-based System Evaluation Plan

Two investigations were proposed to validate the structure and behavior of the knowledge-based application (Chapter 6). The purpose of these evaluations was to prove that the prototype behaves as intended, and to identify design and implementation flaws that should be addressed in subsequent development iterations. Additionally, a study investigating the usability of checklists generated by the prototype was proposed (Chapter 7).

5.3. Results

5.3.1. Knowledge Representation

Figure 5.3 illustrates a high-level graph model that describes the term types (labels) and relationships in the prototype's knowledge base. This model uses 15 term types and 22 relationships to organize medication, regimen, and toxicity domain knowledge in a manner that support seamless reasoning through traversals of the relationships in the model. Medication knowledge (color-coded in green) is represented using the term types **Ingredient**, **Multiple Ingredient**, and **Clinical Drug**, and the relationships *has_ingredient* and *has_part*. Antiretroviral regimen knowledge (color-coded in blue) is represented using the term type **Regimen** and several abstract term types and relationships that describe how regimens are composed of sets of ingredients or sets of clinical drugs, and how they are used clinically. Antiretroviral toxicity knowledge (color-coded in red) is represented using the node **Ingredient Toxicity** which denotes a fact which describes the interaction of several term types engaged in the fact. Accordingly, a given ingredient toxicity fact would be comprised of the ingredient causing the toxicity, the actual toxicity caused, the risk factors of the toxicity, the clinical observations of the toxicity, and the suggested management of the toxicity.

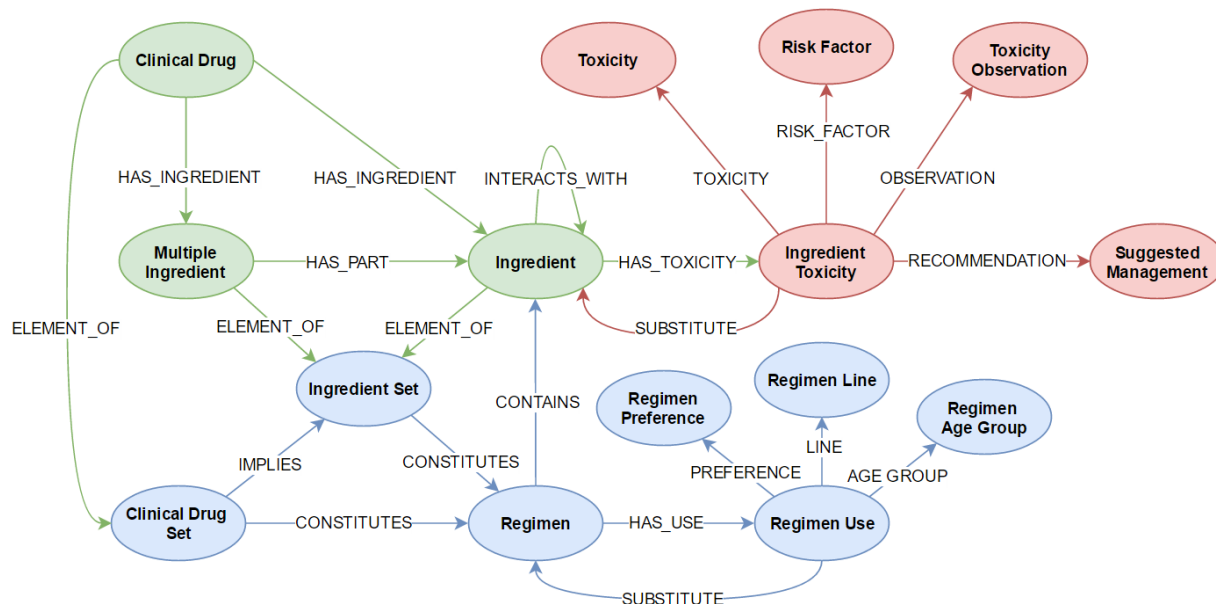


Figure 5.3: High-level graph model for the antiretroviral toxicity domain. Vertices and edges shown in green are related to medications and their ingredients, those in blue are related to antiretroviral regimens, and those in red are related to ingredient toxicities

Figure 5.4 is a more-detailed labeled graph model using an example of abacavir to illustrate how the actual entities and relationships in the knowledge base are conceptually organized. As evident from the model, the **Ingredient**, **Multiple Ingredient**, and **Clinical Drug**, together with the *has_ingredient* and *has_part* relationships are described using standard RxNorm terminology [130]. Some clinical drugs have single ingredients while others have multiple ingredients. For example, the clinical drug *abacavir 300 mg oral tablet* has the single ingredient *abacavir*, while the clinical drug *abacavir 600 mg / dolutegravir 50 mg / lamivudine 300 mg oral tablet* has the multiple ingredient *abacavir / dolutegravir / lamivudine*. Intuitively, each multiple ingredient is comprised of several single ingredient parts. For example, the multiple ingredient *abacavir / dolutegravir / lamivudine* is composed of the parts *abacavir*, *dolutegravir* and *lamivudine*.

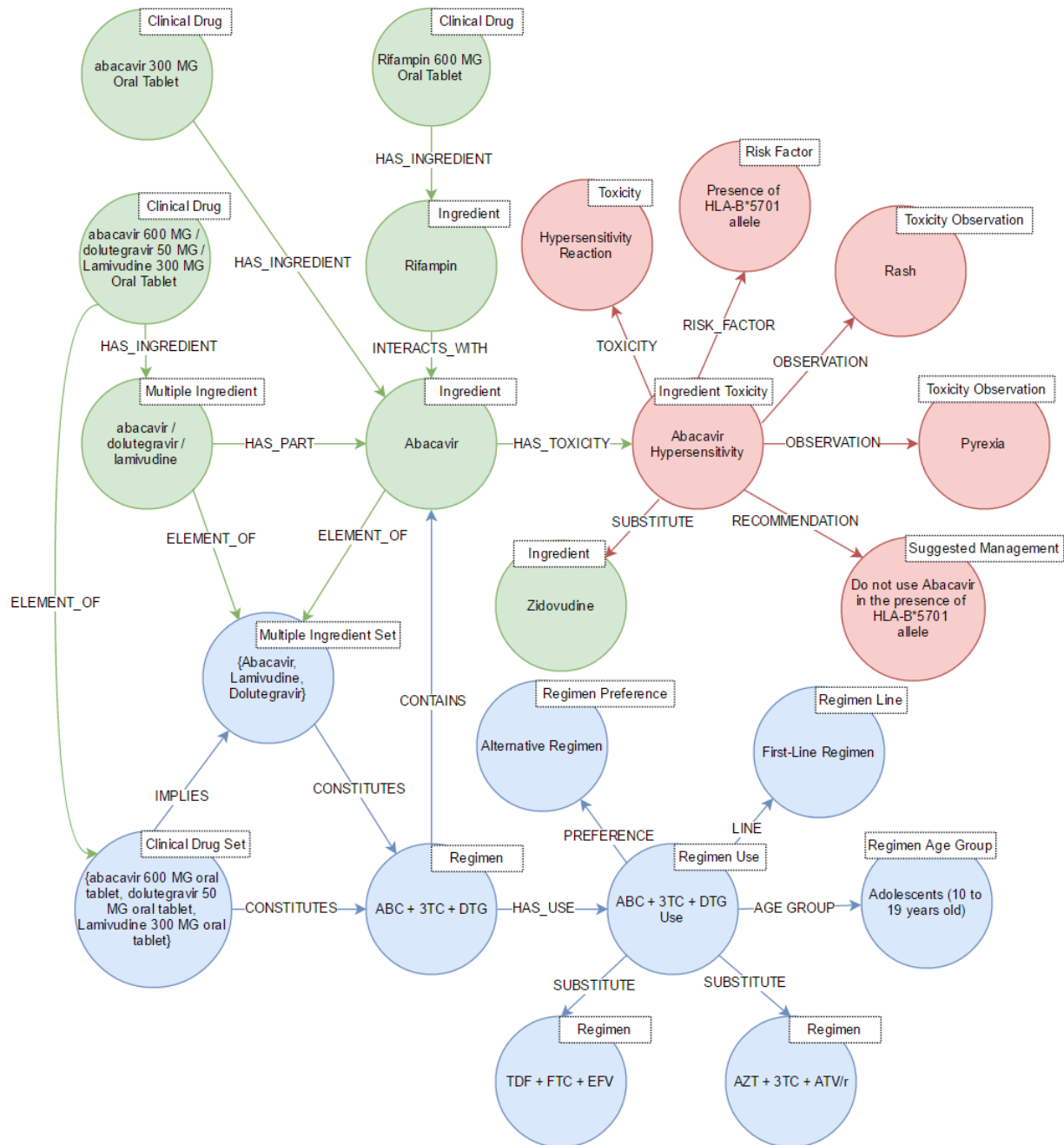


Figure 5.4: Illustration of the knowledge base specification using entities and relationships associated with abacavir-containing medications and regimens. Vertices and edges shown in green are related to medications and ingredients, those in blue are related to antiretroviral regimens, and those in red are related to ingredient toxicities

The vertex **Clinical Drug Set** denotes the fact that individual antiretroviral drugs are elements of unique sets of clinical antiretroviral drugs, and that each set constitutes a specific antiretroviral therapy regimen. For example, *abacavir 600 mg oral tablet* is an element of the set [*abacavir 600 mg oral tablet*, *dolutegravir 50 mg oral tablet*, *lamivudine 300 mg oral tablet*], and this set constitutes the regimen Abacavir (ABC) + Lamivudine (3TC) + Dolutegravir (DTG). Similarly, the vertex **Ingredient Set** was introduced to denote the fact that individual antiretroviral ingredients or multiple ingredients are elements of unique ingredient sets that, in turn, constitute specific antiretroviral therapy regimens. For example, the *abacavir* is an element of the set [*abacavir*, *lamivudine*, *dolutegravir*] which constitutes the regimen ABC + 3TC + DTG.

The vertex **Regimen** denotes a clinically useful combination of antiretroviral drugs. Each **Regimen** has at least one use and can intuitively be thought of as containing more than one ingredient. The vertex **Regimen Use** in the graph denotes the guideline-recommended uses of each regimen. In the model, this vertex represents a regimen use case fact that arises from combination of the vertices **Regimen Preference**, **Regimen Line**, and **Regimen Age Group** that denote the preference (e.g. preferred vs alternative), the line of therapy (e.g. first line vs second-line) and the age group (e.g. Adult vs adolescent) respectively. As an example, the regimen *ABC + 3TC + DTG* is recommended for use as an alternative first-line therapy for adolescents. A regimen use case may have a substitute regimen. For example, among adolescents, *ABC + 3TC + DTG* can be substituted with the first-line *Tenofovir (TDF) + Emtricitabine (FTC) + and Efavirenz (EFV)* or the second-line regimen *Zidovudine(AZT) + Lamivudine (3TC) + Atazanavir / Ritonavir (ATV/r)*.

As previously described, the vertex **Ingredient Toxicity** denotes a fact associated with a specific antiretroviral toxicity instance. This fact relates the **Ingredient**, **Toxicity**, **Risk Factor**, **Toxicity Observation** and **Suggested Management** vertices to denote the causal agent of a given toxicity,

the actual toxicity caused, the risk factors of the toxicity, the clinical observations of the toxicity, and the suggested management of the toxicity respectively. For example, *abacavir* may cause *abacavir hypersensitivity*. Here, the toxicity is *hypersensitivity*, the risk factor is the *presence of the HLA-B*5701 allele*, and examples of toxicity observations include *rash* and *fever*. The recommendation for this toxicity is *do not use abacavir in the presence of HLA-B*5701 allele*. Lastly, *abacavir* can be substituted with *zidovudine*.

5.3.2. System Implementation

Table 5.2 summarizes the pertinent information in the prototype's knowledge base. The knowledge base contains 47 major antiretroviral toxicities caused by 11 antiretroviral ingredients and associated with 41 risk factors. The knowledge base also contains 126 unique manifestations of antiretroviral toxicities that are comprised of 75 signs and symptoms, 11 clinical findings and 40 laboratory findings. In addition to using MedDRA's preferred terms, the signs and symptoms are described using low-level terms and their Swahili translations for local use by lay health providers. For example, the preferred term *pyrexia* is also described using the low-level term *fever* and its Swahili translation *homa*. The knowledge base provides information about 74 unique sets of ingredients that compose 38 different antiretroviral regimens. These regimens are associated with 20 unique uses defined by 4 age group categories (adults (older than 19 years) vs adolescents (10 years to 19 years) vs children (3 years to 9 years), children (younger than 3 years)), 3 preference categories (preferred vs. alternative vs. special circumstance) and 2 therapy line (first-line vs second-line).

A total of 707 out of 974 ($\approx 72.6\%$) unique identifiers were created to describe entities in the knowledge base that could not be found in existing standard vocabularies. Majority of these pertained to the characterization of the composition and use of antiretroviral regimens.

Table 5.2: Definitions, examples, counts (n), sources of term types, and concept identifies in the prototype's knowledge base

| Term Type | Definition | Example | n | Source of Information | Concept Identifiers |
|----------------------|---|--|----------|------------------------------|----------------------------|
| Ingredient | The moiety giving a drug its properties | Abacavir | 11 | WHO | RxCUIs |
| Multiple Ingredient | Preparation with two or more ingredients | Abacavir /dolutegravir / lamivudine | 13 | RxNorm | RxCUIs |
| Clinical Drug | A consumable product (Ingredient + Strength + Dose Form) | Abacavir 300 MG Oral Tablet | 72 | RxNorm | RxCUIs |
| Toxicity | An adverse drug reaction | Hypersensitivity | 45 | WHO | MedDRA codes |
| Ingredient Toxicity | An adverse drug reaction caused by a specific drug | Abacavir Hypersensitivity | 47 | WHO | Identifiers Created |
| Risk Factor | Attribute increasing the likelihood of an ingredient toxicity | Presence of the HLA-B*5701 (risk factor for abacavir hypersensitivity) | 41 | WHO | Identifiers Created |
| Toxicity Observation | Manifestations of an ingredient toxicity | Rash | 126 | AIDSinfo, LiverTox | MedDRA CUIs |
| Suggested Management | Recommendation for an ingredient toxicity | Do not use abacavir in the presence of HLA-B*5701 | 27 | WHO | Identifiers Created |
| Regimen | Combined use of three or more drugs | Abacavir + Lamivudine + Dolutegravir | 38 | WHO | Identifiers Created |
| Ingredient Set | Set of two or more ingredients | [abacavir, lamivudine, dolutegravir] | 74 | Inferred from WHO & RxNorm | Identifiers Created |
| Clinical Drug Set | Set of two or more clinical drugs | [abacavir 600 mg oral tablet, dolutegravir 50 mg oral tablet, lamivudine 300 mg oral tablet] | 451 | Inferred from WHO & RxNorm | Identifiers Created |
| Regimen Use | A fact defining the use of a particular regimen | Abacavir + Lamivudine + Dolutegravir as an alternative first-line regimen for adolescents | 20 | WHO | Identifiers Created |
| Regimen Age Group | Recommended age group for a regimen | Adolescents (10 to 19 years) | 4 | WHO | Identifiers Created |
| Regimen Preference | Priori of a regimen for an age group | Preferred Regimen | 3 | WHO | Identifiers Created |
| Regimen Line | Recommended sequence of therapy | First-line Regimen | 2 | WHO | Identifiers Created |

Table 5.3: Proportion of standard vocabulary concepts in the prototype’s knowledge base not found in the CIEL dictionary used in OpenMRS stratified by term type

| Term Type | Proportion | Missing Concepts |
|----------------------|----------------|---|
| Ingredient | 1/11 (9.1%) | Dolutegravir |
| Multiple Ingredient | 5/13 (38.5%) | Abacavir / Dolutegravir / Lamivudine; Emtricitabine / Rilpivirine / Tenofovir Disoproxil; Cobicistat / Elvitegravir / Emtricitabine / Tenofovir Disoproxil; Atazanavir / Cobicistat; Cobicistat / Darunavir |
| Toxicity | 12/45 (26.7%) | Allergic Hepatitis; Bone Density Decreased; Gastrointestinal Toxicity; Haematotoxicity; Hepatic Enzymes Increased; Hepatitis Flare; Hypersensitivity; Lipohypertrophy; Mixed Liver Injury; Nephrotoxicity; Psychiatric Symptom; Toxic Nephropathy |
| Toxicity Observation | 30/126 (23.8%) | Signs and Symptoms: Blisters; Cold sweat; Fat atrophy; Limb lipoatrophy; Liver tenderness; Peripheral lipodystrophy; Lab Findings: Alanine aminotransferase increased; Ammonia increased; Amylase increased; Aspartate aminotransferase increased; Blood albumin decreased; Blood alkaline phosphatase increased; Blood bicarbonate decreased; Blood creatine phosphokinase increased; Blood creatinine increased; Blood lactic acid increased; Blood phosphorus decreased; Blood uric acid decreased; Eosinophilia; Fractional excretion of phosphate; Glomerular filtration rate decreased; Hepatitis B DNA increased; Hepatitis C RNA increased; High density lipoprotein increased; Lipase increased; Low density lipoprotein increased; Mean corpuscular volume increased; Urinary beta2 microglobulin increased; Urine protein/creatinine ratio increased; Urine retinol binding protein increased |

Table 5.3 describes the standard vocabulary concepts in the prototype’s knowledge base that were not found in the CIEL dictionary used in OpenMRS through mapping. The missing ingredient and multiple ingredient concepts represent medications such as rilpivirine and elvitegravir not commonly found in underserved settings (at the time of development of the prototype). Most of the missing toxicity observations concepts were attributable to categorical interpretations of laboratory findings using MedDRA terms but which could be described using concepts of the

numeric datatype in the CIEL dictionary. For example, *amylase increased* in MedDRA would have a similar meaning to test *amylase* in CIEL having a value larger than its upper limit of normal.

5.4. Discussion

Summary of findings

This chapter describes the objectives and process used for the development of a knowledge-based application prototype designed to address challenges associated with the collection and analysis of antiretroviral toxicity data within HIV care workflows in underserved settings. The prototype functions as diagnostic decision support system [124] and generates outputs that can be used by care providers to confirm or rule out antiretroviral toxicities from patient-reported data. Whereas efforts have been made to apply clinical decision support tools at the point-of-care in underserved settings [14, 15], the work presented in this chapter is one of the first to focus on improving the quality of antiretroviral toxicity monitoring.

The key innovative contribution of this research is the creation of a conceptual model that related knowledge about regimens, ingredients, and toxicities. This is a key addition to the traditional drug information models which describe drug use knowledge based on individual drugs rather than combinations of drugs. Since prescriptions are usually regimen-based, it is critical to understand how toxicities to individual drugs impact the regimen selection. Models like the one described in this chapter would provide a good basis for providing and automating such reasoning.

Other researchers have developed knowledge representations for medication-related information. For example, Sharp ME developed a database of drug-indication relations by aggregating information from raw data in 12 drug information evidence sources [135]. Bousquet et al. created an ontology that maps adverse drug reactions to anatomical locations described in the Foundational

Model of Anatomy (FMA) [136, 137]. The Observational Health Data Sciences and Informatics (OHDSI) collaborative developed a standardized drug knowledge base system called LAERTES that provides pharmacovigilance evidence about the associations between drugs and health outcomes of interest [138]. While all these research efforts have significantly contributed to understanding medication domain knowledge, none of them explicitly models relationships among medications, medication regimens, and adverse reactions as described in this chapter. Accordingly, the model created in this dissertation presents valuable opportunities for future research in medication knowledge management.

Development Challenges

The application of automated CDS technologies at the point-of-care holds the promise of improving care delivery efficiency and effectiveness [100]. However, the construction of knowledge-based applications for supporting antiretroviral toxicity monitoring presents major challenges. For example, knowledge about antiretroviral medications and the toxicities they cause were obtained from different evidence sources. The variations in definitions, meanings, granularities, and interpretations used in the evidence sources, and the lack of automated methods to support knowledge acquisition made the development process difficult and time-consuming. Furthermore, variations were also identified within different sections of the same resources. For example, similar facts were expressed using varied semantics in different sections of structured product labels (e.g., black box warning vs. prescribing section vs. patient counseling information section). Such variations may affect the behavior and analysis of knowledge-based applications [138]. Moreover, in some instances, evidence sources such as clinical guidelines provided vague information that introduced additional work. For example, the WHO guidelines describe the *concomitant use of hepatotoxic drugs* as a risk factor for nevirapine hepatotoxicity. Additional

time and effort was required to identify the list of hepatotoxic drugs whose concomitant use with nevirapine would increase the probability of nevirapine hepatotoxicity.

The need to target diverse groups of users who are likely to have different skills, knowledge, and experiences also presented a challenge in the development of knowledge bases. For example, to facilitate use by both clinicians and lay health workers in the targeted underserved setting, it was necessary to incorporate interface terms and synonyms that closely represents how these cadres would perceive antiretroviral toxicity knowledge. Accordingly, low-level terms and their Swahili language translations were required for the symptom data collection forms intended for use by lay health workers, while more technical terms were used for the reports intended for clinicians.

Challenges in the development of the knowledge base also arose from difficulties associated with the integration of concepts and relationships into the knowledge base. Textual information from evidence sources had to be processed and mapped to MedDRA, RxNorm and UMLS concepts. Additionally, content such as risk factors and antiretroviral regimen information which did not have concepts in standard vocabularies had to be manually curated. Furthermore, due to imperfect mapping between source vocabularies, some relationships between concepts from different sources, e.g., ingredients in RxNorm and toxicities in MedDRA had to be created.

Lastly, the choice of the implementation formalism has a bearing on the difficulty of knowledge base development. For example, implementing complex knowledge models and reasoning in structured query language (SQL) databases may be time intensive and error prone due to the difficulty in designing complex schemas and queries.

Development Limitations

The development process described in this chapter had some limitations. First, due to time and resource constraints, the development of the prototype was conducted by few individuals, over a short period of time, and with minimal involvement of potential end users. However, the goal of the development was to create a viable prototype that forms the foundation upon which future development iterations would be based. Additionally, the development proceeded iteratively with close supervision and crosschecking from domain experts. Second, domain knowledge sources were limited to clinical care guidelines, approved product labels, and domain expert knowledge. However, the selected information sources were relevant, from reputable institutions, and up-to-date. Even so, it is possible that using different sources would result in different structure and behavior of the developed knowledge-based application. Lastly, the current version of the application does not have uncertainty management functionalities. This limits the potential for actual clinical use of the prototype before further development iterations.

5.5. Conclusions

Knowledge-based CDS tools could play a fundamental role in improving the quality of point-of-care antiretroviral toxicity monitoring. However, the success of such tools not only depends on the rigor of their development but also on how they represent domain knowledge. An innovative contribution of the work described in this chapter is the creation and implementation of a model that enables automated reasoning about antiretroviral toxicities caused by medication and regimens. The development process resulted in a stable, functional prototype which could be useful for facilitating the documentation and analysis of antiretroviral toxicity data at the point-of-care. Moreover, the models and artifacts generated from the development process could serve as a basis for the development of similar systems in other disease domains. Additional research is needed to

study uncertainty management functionalities in the application and to investigate more efficient approaches for updating the knowledge base in the prototype. Future work should also focus on the evaluation of structure, behavior, and performance during development iterations and prior to deployment.

Chapter 6. Validating the structure and behavior of a knowledge base implementing clinical guidelines for point-of-care antiretroviral toxicity monitoring

6.1. Introduction

As previously described in Chapter 5, the term ‘knowledge base’ refers to a repository of facts, methods, and models that represent domain knowledge that can be used for problem-solving and analysis of organized data [119]. Consequently, the term ‘knowledge-based system’ refers to a software system that utilizes the knowledge stored in a knowledge-base to analyze problems and provide advice within a restricted domain and in a manner similar to human experts [121]. Knowledge-based systems are foundational applications in biomedical informatics that have remained popular to date [121-123]. Part of the reason for the popularity of knowledge-based systems is the fact that they are particularly useful where symbolic problem solving is preferred over arithmetic or numerical reasoning, as exemplified by the deduction of clinical diagnoses from observations of symptoms and laboratory findings [120, 121].

During the development of a knowledge-based application and before it is deployed for actual use, it is essential to validate that its structure and behavior are free of detrimental design flaws [139]. Validation studies assess the quality of a knowledge-based application by examining the functional completeness and the predictive accuracy of its knowledge base [140]. These evaluations assess whether the knowledge base satisfactorily represents domain knowledge and whether domain experts who did not participate in the development of the knowledge-base application agree that the information, rules, and procedures in the knowledge base are complete and accurate [140]. While structural comparisons evaluate the similarities in how a knowledge base and non-design experts conceptualize and structurally represent knowledge, behavioral validation uses test cases

to evaluate the similarity and compare the accuracy of outputs made by the knowledge base and by non-design experts [139, 140].

In this dissertation, a knowledge-based application prototype that implements standard clinical guidelines for the point-of-care monitoring of antiretroviral toxicities was developed (Chapter 5). The prototype analyzes structured data in a patient's longitudinal electronic health records (EHR) to identify the antiretroviral drugs that the patient is currently using. It then generates a report that describes the risk factors, signs, symptoms, and laboratory findings observed in the EHR that could be related to possible toxicities associated with the identified antiretroviral drugs.

In this chapter, the validation of the structure and behavior of the prototype's knowledge base is described. The goals of the analyses were to ascertain that the prototype's knowledge base contains the correct antiretroviral toxicity domain knowledge and generates patient-specific antiretroviral toxicity reports that are sufficiently accurate for clinical use. The purpose of the structural validation was to quantitatively evaluate whether the concept-concept relationships between the medications, toxicities, and toxicity observations asserted in the prototype's knowledge base were accurate structural representations of domain knowledge. The purpose of the behavioral validation was to quantitatively evaluate the similarity and accuracy of the detection of antiretroviral toxicities, toxicity risk factors, and toxicity observations by the prototype and by non-design experts for a random sample of test cases.

6.2. Methods

6.2.1. Structural Validation

The goal of the structural validation was to compare the concept-concept relationships in the prototype's knowledge base to those provided in publicly available domain drug evidence sources. The smallest unit of the evaluation was defined as a distinct ingredient-condition pair consisting

of an ingredient and an associated health condition of interest, e.g., *Abacavir and Fever*. The main outcome was defined as the proportion of ingredient-condition pairs in the prototype's knowledge base that existed in one or more of the evidence sources used in the study.

The structural validation procedure involved several steps. First, candidate drug knowledge evidence sources for the structural comparisons with the prototype were identified and preprocessed for analysis. After an informal search of published and gray literature, two knowledge sources were identified and included in the study: the Large-Scale Adverse Effects Related to Treatment Evidence Standardization (LAERTES) and the Side Effect Resource (SIDER) 4.1 database. LAERTES is a standardized drug knowledge base system that provides evidence about the associations of drugs with different health outcomes of interest [138]. LAERTES provides evidence from different sources including structured product labels, spontaneous reporting, and biomedical literature [138]. The SIDER 4.1 database provides information extracted from public documents and product labels about marketed medicines and their recorded adverse reactions [141, 142]. In both resources, evidence on adverse drug reactions are identified as pairs of drugs and the associated health conditions (e.g., *Nevirapine-Fever*), and the data can be downloaded via online web portals. In this study, only the data associated with the 11 antiretroviral drugs coded in the prototype's knowledge base (Chapter 5) were extracted from the two knowledge source datasets.

Next, the extracted data were preprocessed by remapping the concept identifiers used in the source knowledge bases to unique RxNorm and UMLS concept identifiers. Ingredient and health condition concepts in the LAERTES dataset are described using unique concept identifiers in the Standard Vocabulary provided by the Observational Health Data Sciences and Informatics (OHDSI) consortium [138, 143]. In this study, the ingredient concept identifiers in LAERTES

were converted to their equivalent RxNorm concept unique identifiers (RxCUIs) using relationships present in the OHDSI Standard Vocabulary. The health condition concepts in LAERTES were first converted to their equivalent SNOMED-CT (Systematized Nomenclature of Medicine – Clinical Terms) codes using relationships present in the OHDSI Standard Vocabulary, and subsequently, to the UMLS concept unique identifiers (CUIs) using relationships present in the UMLS. Ingredient concepts in the SIDER dataset are described using codes derived from PubChem compound identifiers, while the health condition concepts are described using UMLS CUIs associated MedDRA terms. The ingredient identifiers in SIDER were manually converted to the equivalent RxNorm RxCUIs by comparing ingredient names, while the adverse reaction concepts in SIDER were used as provided.

Preprocessing also involved transforming the data set from the prototype’s knowledge base from the ingredient-toxicity-toxicity observation triple format to the ingredient-condition pairs format to enable direct comparisons with relationships present in the evidence sources used in the study. For example, the triple *Abacavir-Hypersensitivity-Fever* was transformed into the ingredient-toxicity pair *Abacavir-Hypersensitivity* and ingredient-observation pair *Abacavir-Fever*.

The final step of the structural validation process was the comparison of the ingredient-condition pairs selected from the prototype and from the evidence sources. The analysis was done in R [144] and involved describing the proportion of ingredient-condition pairs in the prototype that could be found in the evidence sources used. This proportion was computed as the number of ingredient-condition pairs in common between the prototype and a given evidence source divided by the total number of ingredient-condition pairs in the prototype. The analyses were also stratified by knowledge base system (LAERTES vs. SIDER), and by evidence source type (literature vs. spontaneous reporting vs. product label). Manual semantic similarity assessments were conducted

for the ingredient-condition relationships in the prototype that could not be matched to the relationships in LAERTES or SIDER automatically. Lastly, the test for one proportion was used to assess the research hypothesis that >80% of the ingredient-condition relationships in the prototype are equivalent to ingredient-condition relationships present in LAERTES or SIDER.

6.2.2. Behavioral Validation

The goal of the behavioral validation was to evaluate the prototype's ability to detect antiretroviral toxicities, risk factors, and toxicity observations (symptoms, signs, and laboratory findings) from structured patient data. This was achieved by comparing the similarities and the accuracies reports generated by the prototype and by human experts for test cases selected at random. The comparisons were conducted in two forms: a) an unrestricted form in which the universe of possible responses was not restricted, and b) a restricted form in which possible responses were constrained to the knowledge content available in the prototype's knowledge base. The procedural steps used in the study was loosely based on the framework for validation of rule-based systems by Knauf et al. [145] and was in concordance with standard procedures for evaluating knowledge bases [140]. The Knauf framework describes a process involving the generation of test scenarios and the use of a Turing Test-like approach to evaluating the responses of a rule-based system to the test scenarios [145]. The key steps applied in this study were test case generation, test case presentation and experimentation, and data analysis. These steps are described below.

a) Test Case Generation

The first step of the behavioral comparisons was the creation of test cases. In this study, the test cases were derived from raw data in published case reports on antiretroviral toxicities. In October 2016, a literature search was conducted to identify published case reports on antiretroviral toxicities. This search was based on the major types of antiretroviral toxicities described in the

World Health Organization's Consolidated Guidelines [2]. Table 6.1 lists the antiretroviral toxicities of interest. The case reports were identified by electronically searching the Ovid Medline® database. The search strategy involved the use of medical subject heading (MeSH) terms and search strings associated with the antiretroviral toxicities of interest and was limited to case reports having abstracts and published in English between the year 2000 and 2016. Table 6.2 lists the queries used to obtain the case reports. A total of 114 case reports were identified out of which 6 duplicates were removed.

Four reviewers independently reviewed the titles and abstracts of the case report articles retrieved from the search. Each article was independently reviewed by two reviewers, and each reviewer reviewed 54 articles. A fifth reviewer (myself) reviewed all the 108 articles and acted as a tie-breaker during the selection of the articles. The goal of the review was to identify antiretroviral toxicity case reports in which the responsible medication, as well as the patient biodata, signs, symptoms and laboratory findings, were reported. Reviewers were asked to include an article if and only if an adverse drug reaction was reported or described, the culprit drug was mentioned, and the reported case was about HIV/AIDS. They were also asked to identify the case reports that described patient characteristics such as age, gender, and weight as well as signs, symptoms, and laboratory findings. The reviewers were asked to exclude case reports that were solely about the use of antiretroviral medications for the management of hepatitis infections, reports that only addressed treatment efficacies and reports that were about genetics, tumors, or immunotherapy.

The consensus between pairs of reviewers who reviewed the same case reports was estimated using percent agreement and Cohen's Kappa (Table 6.3). The ratings from reviewer 1 were dropped based on the high rate disagreements with the other reviewers. A total of 62 cases were identified from the 55 articles that were eventually included in the study.

Table 6.1: Major antiretroviral toxicities described in the WHO HIV guidelines

| ARV | Toxicity |
|--------------|---|
| Abacavir | <ul style="list-style-type: none"> • Hypersensitivity reaction |
| Atazanavir/r | <ul style="list-style-type: none"> • Electrocardiographic abnormalities (PR and QRS interval prolongation) • Indirect hyperbilirubinemia (clinical jaundice) • Nephrolithiasis |
| Zidovudine | <ul style="list-style-type: none"> • Severe anemia, neutropenia • Lactic acidosis or severe hepatomegaly with steatosis • Lipoatrophy • Lipodystrophy • Myopathy |
| Darunavir/r | <ul style="list-style-type: none"> • Hepatotoxicity • Severe skin and hypersensitivity reactions |
| Dolutegravir | <ul style="list-style-type: none"> • Hepatotoxicity • Hypersensitivity reactions |
| Efavirenz | <ul style="list-style-type: none"> • Persistent central nervous system toxicity (such as dizziness, insomnia, abnormal dreams) or mental symptoms (anxiety, depression, mental confusion) • Convulsions • Hepatotoxicity • Severe skin and hypersensitivity reactions • Gynecomastia • Severe skin and hypersensitivity reactions |
| Lopinavir/r | <ul style="list-style-type: none"> • Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes) • Hepatotoxicity • Pancreatitis • Dyslipidaemia • Diarrhoea |
| Nevirapine | <ul style="list-style-type: none"> • Hepatotoxicity • Severe skin rash and hypersensitivity reaction, including Stevens-Johnson syndrome |
| Raltegravir | <ul style="list-style-type: none"> • Rhabdomyolysis, myopathy, myalgia • Hepatitis and hepatic failure • Severe skin rash and hypersensitivity reaction |
| Tenofovir | <ul style="list-style-type: none"> • Chronic kidney disease • Acute kidney injury and Fanconi syndrome • Decreases in bone mineral density • Lactic acidosis or severe hepatomegaly with steatosis |

Table 6.2: Terms and strategy for literature search in Ovid Medline

| Search | Results |
|--|---------|
| 1 (Abacavir or ABC or Atazanavir or ATV or "ATV/r" or Dolutegravir or DTG or Darunavir or DRV or "DRV/r" or Efavirenz or EFV or Etravirine or ETV or ETR or Lopinavir or LPV or "LPV/r" or Nevirapine or NVP or Raltegravir or RAL or Tenofovir or TDF or Zidovudine or ZDV or AZT).ti. | 15423 |
| 2 ("Drug-Related Side Effects and Adverse Reactions" or "Acidosis, Lactic" or "Acute kidney injury" or "Bone density" or "Drug Hypersensitivity" or "Drug-Induced Liver Injury" or "Fanconi syndrome" or "Fatty Liver" or "Heart Conduction System/abnormalities" or "Muscular Diseases" or "Renal Insufficiency, Chronic" or "Sleep Initiation and Maintenance Disorders" or Anemia or Anxiety or Confusion or Depression or Diarrhea or Dizziness or Dreams or Dyslipidemias or Gynecomastia or Hepatomegaly or Hyperbilirubinemia or Jaundice or Lipodystrophy or Nephrolithiasis or Neutropenia or Pancreatitis or Rhabdomyolysis or Seizures).sh. | 593315 |
| 3 ("adverse drug reaction" or "adverse reaction" or "adverse drug event" or "adverse reaction" or "adverse event" or "toxicity" or allerg\$ or "Abnormal Dreams" or "Acute kidney failure" or "Acute kidney injury" or "Acute renal failure" or "An?emia" or "Bone density" or "bone mineral density" or "breast enlargement" or "Central Nervous System Toxicity" or "Chronic Kidney Disease" or "Chronic Kidney Failure" or "Chronic Kidney Insufficiency" or "Chronic Renal Disease" or "Chronic Renal Failure" or "Chronic Renal Insufficiency" or "Drug-Induced Liver Injury" or "Electrocardiographic abnormalities" or "Enlarged Liver" or "Fanconi syndrome" or "Fatty Liver" or "Heart Conduction disorder" or "Hepatic failure" or "Hepatic Injury" or "Hepatic toxicity" or "Hepatomegaly" or "Hyperbilirubin?emia" or "Icterus" or "Jaundice" or "Kidney Stone" or "Kidney Stones" or "Lactic Acidosis" or "Liver Enlargement" or "Liver failure" or "Liver injury" or "Liver toxicity" or "loose bowel movement" or "Mental symptoms" or "Muscular Disease" or "Nephrolithiasis" or "Neutrop?enia" or "PR interval prolongation" or "QRS interval prolongation" or "QT interval prolongation" or "Renal colic" or "Renal Lithiasis" or "Skin reaction" or "Steatosis" or allerg\$ or Anxiety or Cholesterol or Cholesterol?emia or Confusion or Convulsion? or Depression or Diarrh?ea or Dizziness or Dyslipidemia or Eruptions or Gyn?ecomastia or Hepatitis or Hepatotoxicity or Hypercholesterol?emia or Hypersensitivity or Hypertriglycerid?emia or Insomnia or Lipoatrophy or Lipodystrophy or Myalgia or Myopathy or Pancreatitis or Rash or reaction or Rhabdomyolysis or Seizure? or Triglycerid?emia or Triglycerides).ti,ab,kw. | 2315763 |
| 4 (Didanosine or ddI or Stavudine or d4T or Saquinavir or SQV or Indinavir or IDV or Tipranavir or TPV or Fosamprenavir or FPV or Rilpivirine or RPV or Cobicistat or COBI or Elvitegravir or EVG or Pharmacokinetics or Pregnancy or "Postpartum Period" or Postpartum or Infant or Child or "in vitro" or Prophylaxis or transplant or Transplantation or neonate or "chronic hepatitis B" or Efficacy).ti. | 4470056 |
| 5 animal/ not (human/ and animal/) | 4285612 |
| 6 (1 and (2 or 3)) not (4 or 5) | 2137 |
| 7 limit 6 to (abstracts and english language and "case reports" and yr="2000 - 2016") | 114 |
| 8 remove duplicates from 7 | 108 |

Table 6.3: Inter-rater reliability between reviewers

| Raters | Percent | Kappa |
|-----------------|----------------|--------------|
| rater1 & rater2 | 61.1 | 0.2 |
| rater1 & rater5 | 70.4 | 0.4 |
| rater2 & rater5 | 90.7 | 0.8 |
| rater3 & rater4 | 92.6 | 0.8 |
| rater3 & rater5 | 92.6 | 0.8 |
| rater4 & rater5 | 96.3 | 0.9 |

The 62 cases, available as raw textual narratives, were structured and annotated to enable input and analysis by the prototype developed in the dissertation. The annotation was done using the National Center for Biomedical Ontology (NCBO) Annotator. The NCBO Annotator is an ontology-based web service for annotating raw texts with ontology concepts from several biomedical terminology vocabularies in the Unified Medical Language (UMLS) Metathesaurus and the NCBO Biportal repositories [146, 147]. For example, the text “A female patient using Amoxicillin complained of Rash” would be annotated with several UMLS concepts including *female* (CUI C0086287), *amoxicillin* (CUI C0002645), *rash* (CUI C0015230). The annotation process in this study was done via the NCBO Annotator’s Representational State Transfer (REST) Web Service, with the ontology sources restricted to RxNorm, MEDDRA, and LOINC.

The resulting annotations for each of the 62 cases were manually categorized into 5 categories: descriptive characteristics (e.g., age, weight, gender), comorbidities, medications, signs/symptoms/findings, and laboratory test results. Two reviewers independently reviewed the structured annotations for each case. The goals of this review were to counter check if the annotated concepts were indeed present in the raw text of the case, to identify redundant and synonymous concepts, to add concepts that were not identified by the annotator, and to fill in numeric values and reference ranges for concepts that had numeric values. The two reviewers

compared their reviews for each case with discrepancies solved by consensus after confirmation with the raw text for the case in question. A stratified random sampling procedure was used to select the 15 test cases that were presented to the prototype and the experts in the study. Stratification by the type of antiretroviral medications and the type of antiretroviral drug toxicities was used to minimize sample selection bias.

b) Test case presentation and experimentation

Each test case was described as a pair of input test data and the corresponding output responses. An example of a test case is illustrated in Figure 6.1. The input test data for a given test case was comprised of structured lists of the biodata, comorbidities, medications, signs/symptoms/findings, and laboratory test results. The input data was presented in two formats. In the first format, the test data was presented as observations in an OpenMRS database (MySQL) to enable analysis by the prototype. In the second format, the input data for a given test case was presented as a structured clinical vignette for the human experts using Google Forms. The output for a given test case was defined as lists of 1) Possible antiretroviral toxicities, 2) Possible antiretroviral toxicity risk factors, and 3) Possible antiretroviral toxicity observations (signs, symptoms, and laboratory results).

All the 15 selected test cases were processed by the prototype and 5 human experts who did not participate in the development of the prototype. The prototype processed the input data by querying its knowledge base and generating lists of 1) Ingredient-Toxicity pairs, 2) Ingredient-Toxicity-Risk Factor triples and 3) Ingredient-Toxicity-Toxicity Observation triples. The human experts processed the input data by selecting choices to three multi-answer questions about each test case: 1) What antiretroviral toxicities could plausibly be identified from the case above? 2) What antiretroviral toxicity risk factors could plausibly be identified from the case above? 3) What antiretroviral toxicity manifestations could plausibly be identified from the case above?

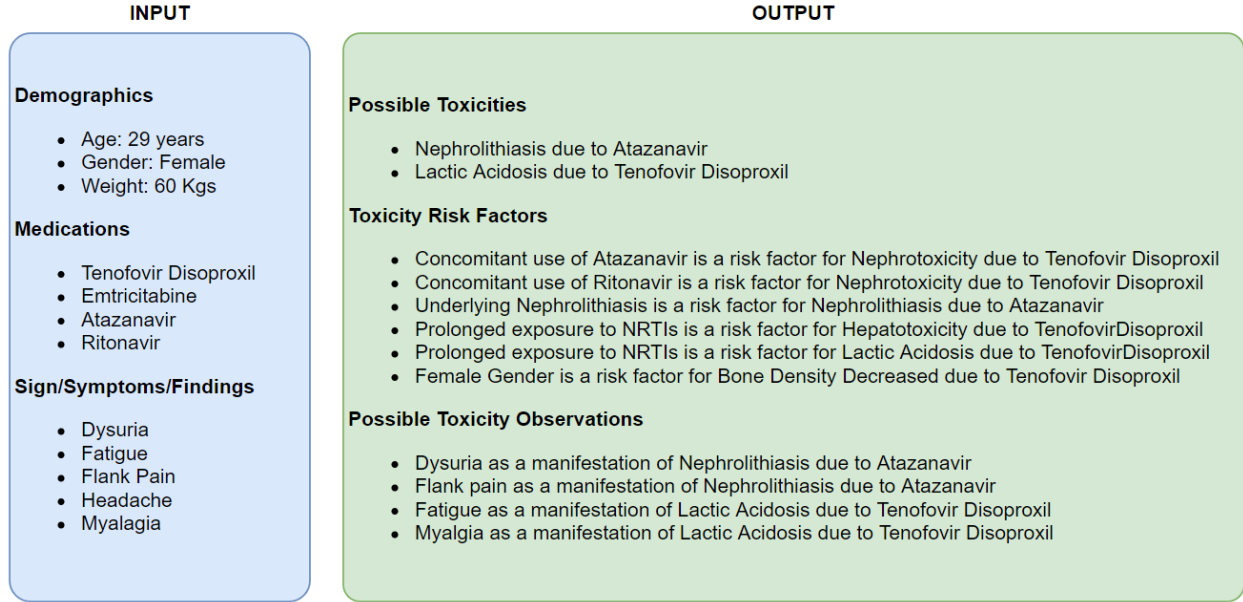


Figure 6.1: Example of the input data (blue) and corresponding output data (green) that constitute a Test Case used in the study.

c) Data Evaluation

The evaluation methodology applied in this study was leveraged from Hripcsak et al.'s foundational work on evaluating the automated detection of clinical conditions from narrative reports using natural language processing [148]. As previously described, the evaluation entailed comparing responses generated by 5 experts and 1 prototype for 15 randomly selected test cases. An additional algorithm that randomly guessed responses with 50% chance of getting the correct answer (based on a majority vote by the experts) was added for comparison. The primary outcome of the behavioral evaluation in this study was the pairwise inter-subject judgmental dissimilarity quantified by the Jaccard distance. Specifically, this distance was defined as one minus the number of response elements in common between the sets of responses by a subject j and a subject k divided by the number of response elements by the two subjects for a given test case i as described in the equation below. The Jaccard distance has a range $0 \leq d_{ijk}(X, Y) \leq 1$ with a higher value implying greater dissimilarity.

$$d_{ijk}(X_{ij}, X_{ik}) = 1 - \frac{|X_{ij} \cap X_{ik}|}{|X_{ij} \cup X_{ik}|}$$

The average Jaccard distance between each pair of subjects was computed as the mean Jaccard distance across all the 15 test cases in the study. For each expert, the mean Jaccard distance from the other 4 experts was computed. For non-expert subjects, the mean Jaccard distance from all the 5 experts was computed. The research hypothesis that the mean Jaccard distance to the group of experts was different for at least one of the subjects was tested using analysis of variance.

The secondary outcome of the behavioral evaluation was the proportion of responses by each subject that were correct, relative to a reference standard based on the majority opinion of the experts. The correctness of responses for a given test case X_i was defined as the number of responses in common between a subject j and the reference standard k divided by the number of responses by the subject:

$$Correctness = \frac{|X_{ij} \cap X_{ik}|}{X_{ij}}$$

Analogous to the dissimilarity evaluation, an expert's reference standard was based on the majority vote of the remaining 4 experts, while the prototype's and random guessing reference standard was based on the majority vote of all the 5 experts. The research hypothesis that there was a difference in the mean correctness of the prototype and the mean correctness of the experts was tested using analysis of variance. In addition to the correctness evaluations, pairwise Kappa statistics were determined to assess consistency in responses between the subjects and the reference standards used.

6.3. Results

6.3.1. Structural Validation Results

Table 6.4 shows the ingredients, conditions and ingredient-condition pairs from the 3 knowledge bases compared in this study. A total of 314 ingredient-toxicity-observation relationships were identified from the prototype's knowledge base. These included 47 ingredient-toxicity pairs and 284 ingredient-observation pairs whose union generated 318 unique ingredient-condition pairs.

Seventy-nine ingredient-condition pairs (25%) in the prototype could not be found in LAERTES or SIDER (Figure 6.2). A majority of the ingredient-condition pairs were confirmed by evidence sourced from spontaneous reporting of adverse effects that were available in the LAERTES knowledge base (Figure 6.3). Only 50% of the relationships were confirmed when using the structured product label knowledge source type, and only 9% were confirmed when using the literature source type (Figure 6.3). Inspection of the 79 ingredient-condition pairs revealed that the discrepancies were due to relationships between 11 ingredients and 42 conditions. However, 42 pairs (53% of the 79 pairs, 13% overall) were confirmed to be genuine relationships described using concepts with different unique identifiers but with similar meanings. For example, the pair *Atazanavir (RxCUI 343047)* and *blood bilirubin increased (CUI C0311468)* in the prototype is semantically similar to *Atazanavir (RxCUI 343047)* and *hyperbilirubinemia (CUI C0020433)* in the evidence sources. Similarly, the pair *tenofovir disoproxil (RxCUI 300195)* and *blood lactic acid increased (CUI C0795692)* in the prototype could be interpreted as *tenofovir disoproxil (RxCUI 300195)* and *lactic acidosis (CUI C0001125)*. Accordingly, only 37 (12%) of the ingredient-condition pairs could not be verified as existent in the evidence sources used. This provided enough evidence to conclude that the proportion of ingredient-condition relationships in the prototype that existed in either LAERTES or SIDER was >80% (p-value <0.001).

Table 6.4: Structural comparison set sizes stratified by knowledge base

| Set | Ingredients | Conditions | Ingredient-Condition Pairs |
|-----------|-------------|------------|----------------------------|
| Prototype | 11 | 117 | 318 |
| SIDER | 10 | 283 | 604 |
| LAERTES | 11 | 4290 | 23706 |

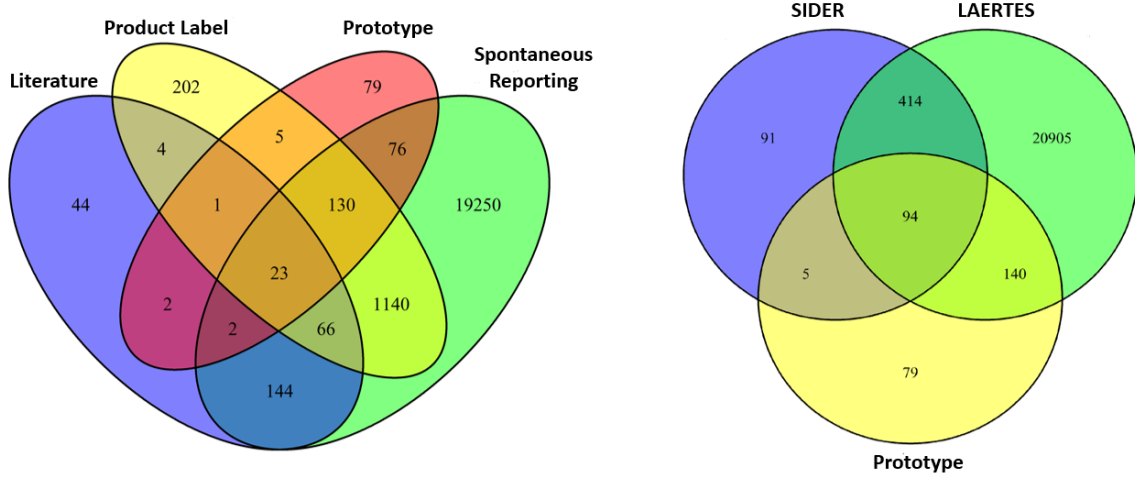


Figure 6.2: Overlaps between the sets of ingredient-condition pairs in the prototype and in selected evidence source types (left) and evidence knowledge bases (right). (Set sizes not drawn to scale)

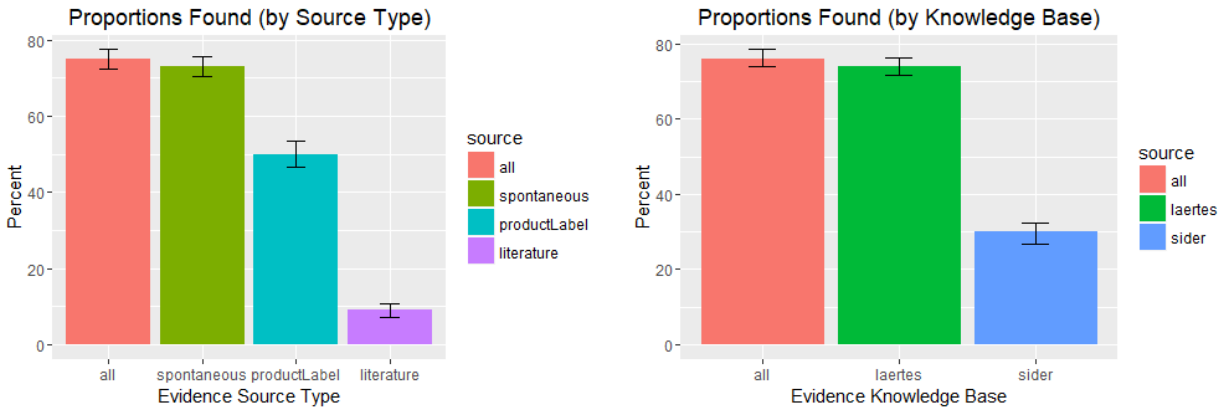


Figure 6.3: Proportion of ingredient-condition pairs in the prototype verified as existent in selected evidence source types (left) and evidence knowledge bases (right).

6.3.2. Behavioral Validation Results

The 5 experts and the prototype generated 314 unique responses from the 15 test cases. Of these responses, 66 were about antiretroviral toxicities, 109 were about risk factors, and 139 were about toxicity observations. Based on the majority opinion of the experts, 199 responses (63%) were considered correct. Of the 314 responses generated, 70 responses (22%) did not exist as evidence in the prototype's knowledge base.

The mean Jaccard distances of each subject from the experts are illustrated in Figure 6.4. The comparisons between the mean Jaccard distances of each subject and the mean Jaccard distance of the experts are provided in Table 6.5. Although the experts differed in their interpretation of the test cases for at least 25% of the time, the differences in the Jaccard distances of the experts from each other was not statistically significant. This observation was confirmed by a Fleiss's Kappa score of 0.77 that indicated substantial agreement among the 5 experts. When all the responses were accounted for (unrestricted), the mean Jaccard distance of the experts from each other was 0.312 (95% CI, 0.283 to 0.342), while the mean Jaccard distance of the prototype from the experts was 0.424 (95% CI, 0.382 to 0.466). The difference between these two distances was 0.112 (0.06 to 0.163, p-value <0.001) suggesting statistically significant differences between responses by experts and by the prototype. However, the distance of the prototype and the experts was smaller than the distance between the prototype and random guessing at 50% chance of being correct (Figure 6.4 - unrestricted). Interestingly, restricting the universe of responses (by ignoring the 70 responses that did not exist in the knowledge base for all subjects) resulted in the difference between the distance of the prototype from the experts and the average distance among the experts becoming statistically indiscernible. The removal of the responses did not appear to significantly affect the distances of the other subjects from the experts (Figure 6.4 - restricted).

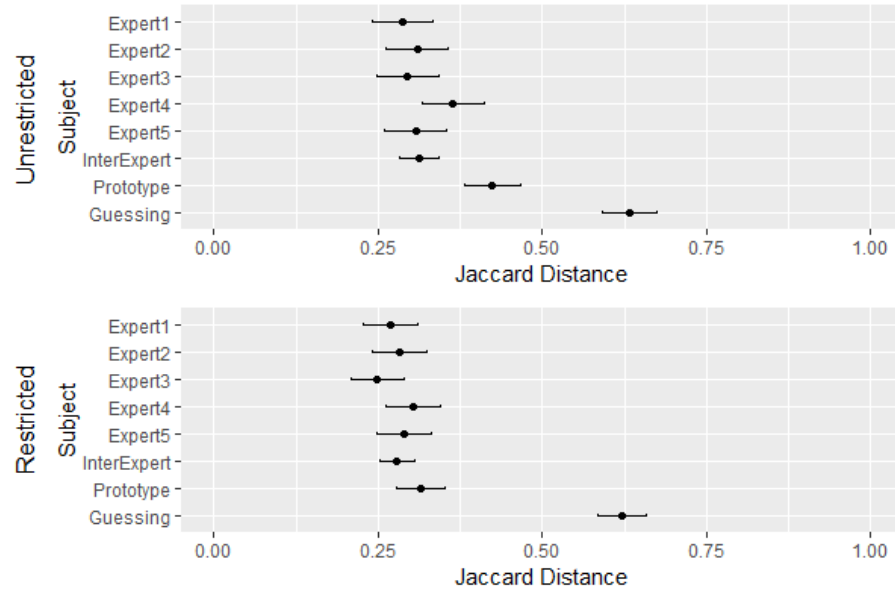


Figure 6.4: Mean Jaccard Distance (and 95% Confidence Interval) of Subjects from Experts for unrestricted responses (top) and restricted responses (bottom)

Table 6.5: Differences between Mean Subject and Mean Expert Jaccard Distances

| Category | Subject | Difference (95% CI) | p-value |
|--------------|-----------|--------------------------|---------|
| Unrestricted | Expert 1 | -0.025 (-0.081 to 0.03) | 0.357 |
| | Expert 2 | -0.003 (-0.059 to 0.052) | 0.904 |
| | Expert 3 | -0.018 (-0.073 to 0.038) | 0.52 |
| | Expert 4 | 0.051 (-0.004 to 0.107) | 0.067 |
| | Expert 5 | -0.005 (-0.06 to 0.05) | 0.851 |
| | Prototype | 0.112 (0.06 to 0.163) | <0.01* |
| | Guessing | 0.321 (0.27 to 0.372) | <0.01* |
| Restricted | Expert 1 | -0.01 (-0.059 to 0.039) | 0.685 |
| | Expert 2 | 0.004 (-0.045 to 0.053) | 0.88 |
| | Expert 3 | -0.03 (-0.078 to 0.019) | 0.227 |
| | Expert 4 | 0.025 (-0.024 to 0.074) | 0.312 |
| | Expert 5 | 0.011 (-0.038 to 0.06) | 0.648 |
| | Prototype | 0.037 (-0.009 to 0.082) | 0.108 |
| | Guessing | 0.342 (0.297 to 0.387) | <0.01* |

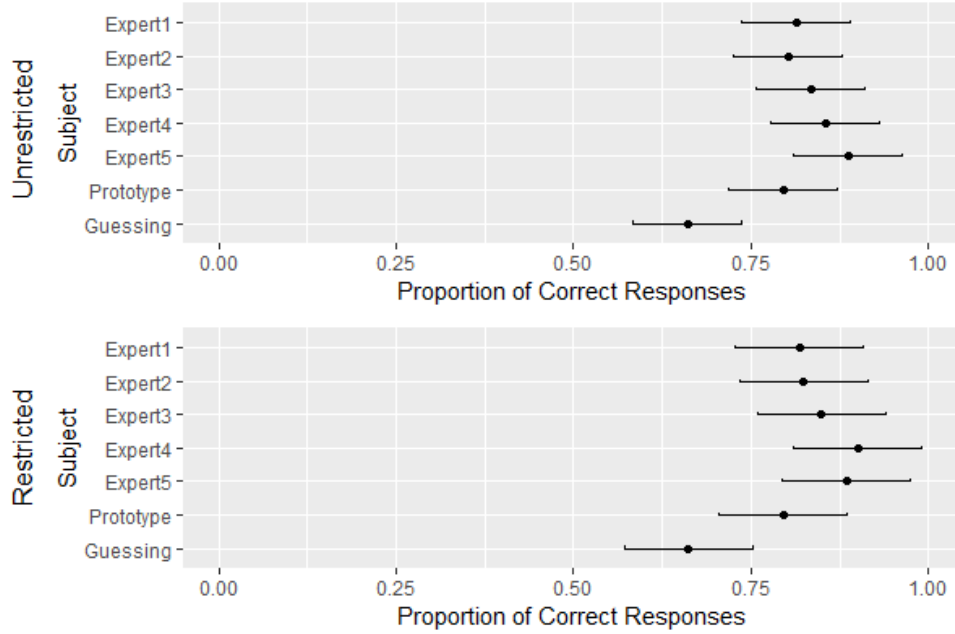


Figure 6.5: *Proportion of Correct Responses (and 95% Confidence Interval) of Subjects from Experts for unrestricted responses (top) and restricted responses (bottom)*

Figure 6.5 illustrates the means and 95% confidence intervals for the proportion of correct responses by a subject. When responses were unrestricted, the mean correctness of the prototype across all test cases was 79.5% (95% CI, 71.9 to 87.2). Based on inspection of the confidence interval overlaps and on the one-way ANOVA model using all subjects, there was insufficient evidence to conclude that difference between the mean correctness of the prototype and the mean correctness of the human experts was statistically significant ($p\text{-value} > 0.5$). Similar conclusions were found when the responses were restricted. Lastly, a Cohen's Kappa score of 0.68 indicated moderate agreement between the prototype's responses and reference standard responses derived from the majority opinion of the experts. These observations collectively suggest that the fact that the prototype's accuracy is equivalent to human expert accuracy cannot be ruled out.

6.4. Discussion

6.4.1. Structural Validation

The structural validation conducted in this study entailed comparing the semantic representation of ingredient-condition relationships in the prototype to representations in two publicly available adverse drug reaction evidence knowledge bases. The findings of the investigation suggest that up to 88% of antiretroviral ingredient-condition pairs independently curated and standardized from current treatment guidelines and drug labels could be verified through direct structural comparisons (75%) and additional manual semantic similarity comparisons (13%) with the concept-concept relationships in publicly available drug safety evidence knowledge bases.

The fact that about 12% concept-concept relationships in the prototype's knowledge base could not be validated by comparisons between existing knowledge evidence sources can be explained by three main reasons. First, it is plausible that some of the relationships in the prototype's knowledge base were valid despite not being structurally equivalent to the comparable relationships in the evidence sources used. Structural differences between some relationships in the prototype and in the evidence sources used were attributable to concepts assigned different unique identifiers despite being similar in meaning (e.g., *blood bilirubin increased (CUI C0311468)* and *hyperbilirubinemia (CUI C0020433)*). This redundancy could be due to semantic heterogeneity – where schema and data set development by independent parties within the same domain introduces differences in meaning and interpretation of data elements [149]. This observation is backed by the fact that significant proportions of the different evidence sources used in this study did not overlap. Boyce and his colleagues outline several sources of variability during the process of extracting, translating, and loading drug safety information into knowledge bases and how these could influence downstream analysis [138]. For example, when extracting drug

toxicity information from product labels, decisions such as whether to obtain information from anywhere on the label or from specific sections of the label (e.g. black box warning vs. prescribing section vs. patient counselling information section) could determine the types of concepts and relationships that are eventually included in a drug safety knowledge base. Knowledge acquisition decisions to use technical terms such as ‘angioedema’ in the prescribing section, to use lay terms such as ‘lip swelling’ in the patient information section, or to include both could introduce semantic heterogeneity among different evidence sources without necessarily making the information invalid. A second plausible explanation for the variations in ingredient-condition relationships among different evidence sources is the novelty of the asserted associations. Voss et al. explain that novel ingredient-condition associations are likely to appear faster in source evidence source types such as spontaneous reporting evidence sources compared to other sources types such as literature [150]. Using a similar reasoning, because the content of the knowledge base evaluated in the study was derived from the drug labels and clinical guidelines that were more recent (2016) compared to the evidence sources (e.g., current version of SIDER was released in 2015), it is possible that the relationships that were not found in the sources were legitimate but are yet to be updated in the evidence sources. Lastly, it is possible that the relationships in the evaluated knowledge base could not be confirmed because they were genuinely erroneous.

Structural comparison studies are usually conducted to evaluate the similarities in how a knowledge base and non-design experts conceptualize and structurally present knowledge [140]. This study demonstrates that in the absence of domain experts, it is possible to use existing informatics evidence resources to evaluate independently-constructed knowledge bases. Domain experts could complement this evaluation approach by delineating sources of variability that cannot be directly explained by structural comparisons between knowledge base contents.

6.4.2. Behavioral Validation

The behavioral validation conducted in this study involved comparing the detection of antiretroviral toxicities, risk factors, and observations (signs, symptoms, and laboratory findings) by the prototype and by non-design experts for a random sample of test cases. The findings of this study suggest that knowledge base of the prototype developed in this dissertation behaves as human domain experts albeit to a moderate degree.

There was sufficient evidence to conclude that there was a statistical difference in the detection of antiretroviral toxicities, risk factors, and observations (sign, symptoms, and laboratory findings) from structured data between the prototype and human experts. Nonetheless, the reports generated by the prototype tended to be more similar to human expert reports than to reports generated through random guessing. The accuracies of the prototype and the human experts were indistinguishable.

Interestingly, when the universe of responses was restricted to the knowledge that was available in the prototype, the dissimilarities between the reports generated by the prototype and the human experts became indistinguishable, while the dissimilarities among reports generated by the experts remain unchanged. This observation confirms the well-known assertion that for a knowledge base to be considered functionally complete, it must not only be structured appropriately and contain accurate knowledge, but it must also have adequate coverage of the domain knowledge [140]. However, as was the case with the development of the prototype in this dissertation, it is not always possible or reasonable to ensure complete domain coverage particularly in the early stages of the development of knowledge-based applications. Furthermore, when using standard guidelines as the basis for the content of the knowledge base of knowledge-based applications, inadequate

domain coverage is likely. This is because care guidelines tend to provide content about key treatment-limiting conditions that are most impactful in clinical care.

It was also interesting to observe that although the dissimilarities of reports among the experts were statistically indistinguishable, the proportion of time they disagreed with each other was as high as 25%. This suggests variability in the manner in which experts interpret antiretroviral toxicity information albeit the fact that no single expert is significantly different from the others. Hripcsak et al. reported a similar observation among expert physicians identifying conditions from radiology reports [148]. In the study described in this chapter, it was not clear why the experts interpreted the reports differently and if this affected the performance of the prototype. Future research should investigate this phenomenon further. A plausible approach would involve comparing the performance of the prototype against a set of true reference standard responses rather than one based on the majority opinion of experts working independently.

6.4.3. Limitations

This study had several limitations. First, for the structural validation, only two publicly available knowledge bases were used. It is possible that using different evidence sources would result in different conclusions. Second, for the behavioral validation, only pharmacists were used as expert subjects. Using experts from other cadres could have resulted in different conclusions. Nonetheless, the experts used were carefully selected, had sufficient experience, and did not participate or have vested interests in the development of the prototype. The results generated by the study are, therefore, credible but may not be extended to other health cadres. Lastly, the evaluated application was an initial prototype. It is possible that as the iterative development of the application continues, future conclusions about its structure and behavior would change.

6.5. Conclusions

Overall, this study suggests that it is possible to implement antiretroviral toxicity domain knowledge in knowledge-based applications successfully and that such applications have the potential to support automated detection of antiretroviral toxicities, risk factors and observations (signs, symptoms, and laboratory findings) from structured patient records. The research also points to the potential value of using disparate evidence sources to validate the structure and content of independently-developed knowledge bases. This is, however, with the caveat that factors such as semantic heterogeneity and novelty of associations are likely to affect the outcomes of such endeavors, and that future research is needed to investigate the role of informaticians in addressing these concerns. Finally, future informatics research should investigate the impact of the variability among expert subjects on the outcomes of studies investigating the behavior of knowledge-based applications.

Chapter 7. Assessing the Usability by Peer Health Workers of Computer-Generated Checklists for Point-of-Care Antiretroviral Toxicity Symptom Documentation

7.1. Introduction

Point-of-care antiretroviral toxicity monitoring promotes the detection and early intervention of antiretroviral side effects and adverse drug reactions [2]. The World Health Organization (WHO) encourages HIV care programs to conduct routine antiretroviral toxicity monitoring. This would provide more accurate data for the determination of incidence, clinical relevance, and impact of antiretroviral toxicities [2]. Current clinical practice guidelines recommend a symptom-directed approach to antiretroviral toxicity monitoring [2, 22]. This involves the clinical assessment of signs and symptoms attributable to specific antiretroviral toxicities at the point-of-care, with laboratory testing suggested but not mandatory for high-risk patients using certain drugs [2].

The symptom-directed approach to routine antiretroviral toxicity monitoring is particularly useful in underserved settings which lack the capacity to conduct laboratory testing [2]. However, the approach is laborious and, therefore, difficult to implement in underserved settings which are characterized by poor healthcare infrastructure and competition for scarce human and financial resources [11, 12]. Accordingly, in order to successfully implement the symptom-directed approach in underserved settings, practical methods that address setting-specific workforce challenges would be required.

A plausible approach to alleviating the workforce-related barriers to symptom-directed antiretroviral toxicity monitoring is task shifting. Task shifting refers to the delegation of tasks from skilled professionals to more readily available lay health workers and is an accepted strategy for mitigating health workforce challenges in underserved settings [16, 17]. An increasingly

popular task shifting approach involves the use of peer health workers [23, 37]. A peer is a person who has a shared living experience as another person [23]. Consequently, peer health workers have similar clinical and medication experiences as the persons they care for [37]. For example, in HIV care, peer health workers would be HIV-positive persons who have demonstrated competence in HIV self-management, clinic attendance, and medication adherence [38]. They would be trained and remunerated to take up new responsibilities such as counseling, education, and data collection [23]. Previous studies have demonstrated that delegating tasks to peer health workers could improve clinical data collection and enhance patient engagement through education and psychosocial support [151-154].

It is, therefore, reasonable to postulate that point-of-care antiretroviral toxicity monitoring using the symptom-directed approach could be enhanced by redistributing symptom data collection tasks to peer health workers. Furthermore, it is logical that the efficiency and effectiveness of such task delegation could be enhanced using standardized documentation tools such as checklists. Unfortunately, research on leveraging peer health workers to support point-of-care data collection using standardized documentation tools has received little attention. For example, although several data collection instruments including scales, profiles, and checklists are well-described in the biomedical literature [24, 25], neither their usability, nor their feasibility, nor their impact when used by lay health workers collecting antiretroviral toxicity data has been studied adequately.

This chapter reports the findings of a study that investigated the usability of computer-generated checklists for documenting antiretroviral toxicity symptoms as perceived by peer health workers based in an underserved setting in western Kenya. The objectives of the study were to assess the level of satisfaction with the checklists and the cognitive mental effort required to complete the

checklists as perceived by peer health workers. The study also identified the main sources of documentation errors that informed the redesign of the checklists.

7.2. Methods

7.2.1. Study Design

This study was designed as a quantitative usability test. The goal of usability testing is to determine end-user satisfaction with a product or service and to identify usability problems that need to be addressed [155]. In this study, the usability of computer-generated checklists for documenting antiretroviral toxicity symptoms was investigated. Testing consisted of peer health workers using the checklists to document symptoms described in 5 case scenarios and providing feedback on their usability experiences. The primary outcome of the study was the level of satisfaction with the checklists as measured by the System Usability Scale (SUS) [156, 157]. To determine if the usability of the checklists was acceptable, the research hypothesis that the mean SUS score is >68 was tested. The secondary outcome of the study was the level of mental effort needed to complete checklist documentation case scenarios as measured by the Subjective Mental Effort Question (SMEQ) [157, 158]. To determine if the checklists are not difficult to use, the research hypothesis that median SMEQ score is <20 was tested. Other outcomes investigated included time to case completion, case completion rates, and sources of documentation errors [159].

7.2.2. Checklists


In this dissertation, an electronic knowledge-based application prototype that implements standard guidelines for antiretroviral toxicity monitoring was developed (see Chapter 5). In addition to other functionalities, this prototype generates checklists that can be used for documenting symptoms and subsequently recognizing possible antiretroviral toxicities experienced by individual patients. The contents of the checklists are based on antiretroviral toxicities described in the standard clinical

guidelines on the use of antiretroviral drugs [2, 6] and in approved drug labels [126]. The contents of the checklists are customized based on the antiretroviral regimen used by a patient. For example, the checklist for a patient using a regimen consisting of Tenofovir + Lamivudine + Efavirenz is different from the checklist for a patient using a regimen consisting of Abacavir + Emtricitabine + Nevirapine. To create a checklist for a given patient, the prototype queries the patient's longitudinal electronic health record (EHR) data and identifies the antiretroviral medications currently used by the patient. The prototype uses the identified medications to query its knowledge base and subsequently generate the contents of the checklist.

Figure 7.1 shows an example of a printable checklist generated by the prototype. To use this 'low-tech' version of the checklist, the user first checks off entries in the signs/symptoms list. Next, guided by the colored lines mapping the symptoms to adverse reactions, the user tallies the symptom counts associated with each possible adverse drug reactions, and inserts the counts in the appropriate field. Completed checklists are intended for use by clinicians to confirm or rule out possible adverse reactions and guide subsequent management.

7.2.3. Case Scenarios

The case scenarios used in this study were presented as clinical vignettes depicting patients complaining of symptoms experienced after using specific antiretroviral therapy. The contents of the clinical vignettes were derived from data provided in published antiretroviral toxicity case reports. To generate the case scenarios, a stratified random sample of 5 test cases was selected from the 62 antiretroviral toxicity test cases created in Chapter 6 (section 6.2.2) of this dissertation. Stratification was based on the drug regimen type and the number of symptoms per test case to mimic variations in real clinical scenarios. Next, the 5 selected test cases were used to create the 5 textually narrated case scenarios used in this study. Table 7.1 illustrate these case scenarios.

| | | |
|---|--|-------------------------------|
|  | Antiretroviral Toxicity Symptom Screening Checklist | Thu May 18 2017 |
| First Name: <u>Amanda</u> | Last Name: <u>Uwayezu</u> | Person Id: <u>1490</u> |

Check off signs/symptoms

| | |
|---|---|
| <p>Arthralgia: Pain in the joints (Kuumwa na viungo) <input type="checkbox"/></p> <p>Blister: Blisters on the skin (Malengelenge) <input type="checkbox"/></p> <p>Chromaturia: Dark-colored urine (Mkojo ulio na rangi nyeusi) <input type="checkbox"/></p> <p>Conjunctivitis: Redness or inflammation of the eyes (Uwekundu au uvimbe wa macho) <input type="checkbox"/></p> <p>Decreased appetite: Loss of appetite (Kukosa hamu ya kula) <input type="checkbox"/></p> <p>Dizziness: Feeling dizzy or lightheaded (Kizunguzungu) <input type="checkbox"/></p> <p>Dyspnoea: Trouble breathing (Tatizo la kupumua) <input type="checkbox"/></p> <p>Facial wasting: Fat loss in face (Upungufu wa mafuta usoni) <input type="checkbox"/></p> <p>Faeces pale: Pale stools (Kinyesi nyeupe nyeupe) <input type="checkbox"/></p> <p>Fatigue: Feeling tired (Uchovu) <input type="checkbox"/></p> <p>Hepatomegaly: Enlargement of the liver (Ini kuvimba) <input type="checkbox"/></p> <p>Jaundice: Yellowing of skin (Ngozi kuwa manjano) <input type="checkbox"/></p> <p>Limb lipoatrophy: Loss of fat from arms and legs (Upungufu wa mafuta mikononi na miguuni) <input type="checkbox"/></p> <p>Malaise: Generally feeling sick (Hisi kuwa mgonjwa) <input type="checkbox"/></p> <p>Muscular weakness: Muscle weakness (Udhaifu wa misuli) <input type="checkbox"/></p> <p>Myalgia: Muscle pain (Kuumwa na misuli) <input type="checkbox"/></p> <p>Nausea: Feeling like vomiting (Hamu ya kutapika) <input type="checkbox"/></p> <p>Ocular icterus: Yellowing of the eyes (Macho kuwa manjano) <input type="checkbox"/></p> <p>Palpitations: Irregular heartbeat (Mdundo mmbaya wa moyo) <input type="checkbox"/></p> <p>Peripheral coldness: Feeling cold in arms and legs (Baridi mikononi au miguuni) <input type="checkbox"/></p> <p>Pyrexia: Fever (Kiwango cha juu cha joto (Homa)) <input type="checkbox"/></p> <p>Rash: Rash (Vipele kwa ngozi) <input type="checkbox"/></p> <p>Right upper quadrant pain: Pain in the right upper abdomen (Maumivu ya tumbo upande wa kulia chini ya ubavu) <input type="checkbox"/></p> <p>Stomatitis: Blisters, hives, or sores in the mouth (Malengelenge midomoni au kinywani) <input type="checkbox"/></p> <p>Swelling face: Swelling of the face (kuvimba uso) <input type="checkbox"/></p> <p>Vomiting: Vomiting (Kutapika) <input checked="" type="checkbox"/></p> | <p style="text-align: center; margin-bottom: 10px;">Sign/Symptom counts</p> <div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> <p style="text-align: center; margin: 0;">Hepatotoxicity</p> <p style="text-align: center; margin: 0;">Nevirapine</p> </div> <div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> <p style="text-align: center; margin: 0;">Hepatotoxicity</p> <p style="text-align: center; margin: 0;">Zidovudine</p> </div> <div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> <p style="text-align: center; margin: 0;">Hypersensitivity Reaction</p> <p style="text-align: center; margin: 0;">Nevirapine</p> </div> <div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> <p style="text-align: center; margin: 0;">Lactic Acidosis</p> <p style="text-align: center; margin: 0;">Zidovudine</p> </div> <div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> <p style="text-align: center; margin: 0;">Lipoatrophy</p> <p style="text-align: center; margin: 0;">Zidovudine</p> </div> <div style="border: 1px solid black; padding: 5px;"> <p style="text-align: center; margin: 0;">Myopathy</p> <p style="text-align: center; margin: 0;">Zidovudine</p> </div> |
|---|---|

Figure 7.1: Example of a checklist generated from the record of a single patient. The records used are deidentified and date-shifted

Table 7.1: Usability testing case scenarios

| Id | Clinical Vignette |
|-----------|---|
| Case 1 | I am Hamish Rugendo, and my person ID number is A0123453. I have been using Zidovudine, Lamivudine, and Efavirenz for about 10 days. I decided to come to the clinic today because I noticed a rash on my trunk and arms after taking my medications. My skin feels itchy, and my eyes are reddish. In addition, I started having muscle pains and feeling very tired which is not normal for me. Also, I feel like I have a fever. |
| Case 2 | I am Lucy Cheptoo, and my person ID is A26744789. I was started on Abacavir, Lamivudine, Atazanavir, and Ritonavir two years ago and I have been using the regimen since then. Recently, I have been feeling pain on the left side of my body between my abdomen and my back. I have also been vomiting and feeling like I have a fever. |
| Case 3 | My name is Kelly Rukira. My person ID is A12312863. I had been using Abacavir, Lamivudine, and Efavirenz for about 15 days when I started having feelings of tiredness and general sickness. I later developed a rash, fever, and muscle pains, and decided to come to the clinic to be evaluated. |
| Case 4 | My name is Darius Manyika, and my person ID is A0756908. I was started on Zidovudine, Lamivudine, and Nevirapine three weeks ago. I have now developed fever, pain in the right upper part of my abdomen, nausea, vomiting, and diarrhea. My skin has started turning yellowish, and I think my liver is getting larger. |
| Case 5 | My name is Susan Virunga, and my ID is A50121845. I have been using Tenofovir, Emtricitabine, Lopinavir / Ritonavir and Septrin for more than 1 year. I recently started feeling a lot of pain in my bones. My muscles have also been feeling weak. |

7.2.4. Study Setting

This study was conducted at the Academic Model Providing Access to Healthcare (AMPATH) in Eldoret western Kenya. AMPATH is an umbrella healthcare organization formed as a result of the collaboration between Moi University College of Health Sciences, Moi Teaching and Referral Hospital and a consortium of North American Academic Medical Centers led by Indiana University School of Medicine [77]. The academic centers that constitute AMPATH pursue the tripartite mission of care, training, and research with the overarching goal of addressing short- and long-term challenges in global health. AMPATH works in partnership with the Government of Kenya to provide HIV care at its primary site in Eldoret, Kenya and via more than 25 satellite clinics throughout western Kenya. Since its inception, AMPATH has provided care to about 180,000 HIV/AIDS patients, with almost 2,000 new HIV patients being enrolled each month [78].

AMPATH has expanded from its initial clinical focus on HIV/AIDS to encompass chronic disease care, primary health care, and specialty healthcare. To address the healthcare workforce challenge brought about by this scale up, AMPATH is actively researching and implementing different task redistribution paradigms including peer-driven HIV counseling and pharmacovigilance [160].

7.2.5. Study participants

Participants in this study were peer health workers trained and remunerated by AMPATH. All peer health workers at AMPATH were eligible for participation regardless of their qualifications, work experience, or job functions. All potential participants were invited to participate in the study. The recruitment target was set to at least five participants as this sample size is sufficient for usability testing during the early stages of the development of the tool to be tested [161].

7.2.6. Data Collection

A high-level description of the data collection procedure is shown in Figure 7.2. First, participants completed a demographics questionnaire that was administered to collect information about the age, gender, level of education, and job roles (Appendix 7.1). Next, participants completed a symptom knowledge questionnaire which asked participants to describe 10 randomly-selected antiretroviral toxicity symptom terms in English or Swahili (Appendix 7.2). Prior to attempting the actual usability task, participants received practice on reading case scenarios and completing checklists as was intended (Appendix 7.3). Actual testing consisted of each participant completing each case scenarios included in the study as follows. First, the participant read the case scenario's vignette to identify the reported symptoms. Next, participant checked off the identified symptoms on a checklist provided for the case scenario. Finally, guided by the colored lines mapping the symptoms to adverse reactions on the checklist, participants tallied the symptom counts associated with each possible adverse drug reactions and inserted the counts in the appropriate field.

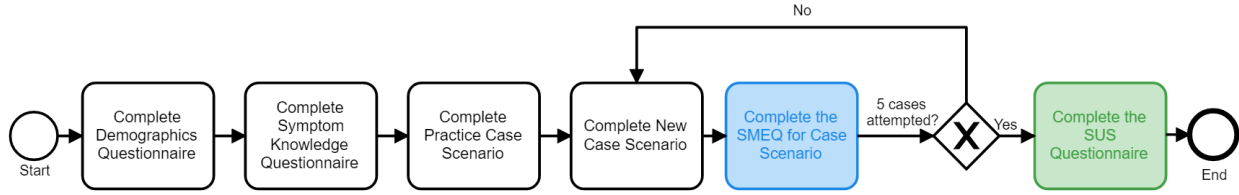


Figure 7.2: High-level description of the data collection workflow (participant's perspective)

Immediately after completing each case scenario, participants completed SMEQ questionnaire to score the level of mental effort they required to complete the case. The SMEQ is a single item cognitive workload questionnaire that assesses perceived task difficulty on a scale of 0 to 150 points that correspond to nine labels ranging from “Not at all hard to do” to “Tremendously hard to do”(Appendix 7.4) [157]. A research assistant recorded the start time (when a case was handed over to the participant) and the finish time (when the finished case was received back from the participant) to collect data for analyzing time to case completion.

Immediately after completing all 5 case scenarios, participants completed the SUS questionnaire to collect data on the participant's perceived satisfaction with the checklists. The SUS is a ten-item post-study questionnaire with responses coded as five-level Likert items from “Strongly Disagree” to “Strongly Agree” (Appendix 7.5) [157].

7.2.7. Data Analysis

Quantitative statistical analyses were conducted in R [144]. Descriptive statistics of the participants' characteristics were expressed as proportions, medians, and interquartile range. To generate the symptom knowledge score, two assessors independently reviewed each participant's symptom knowledge questionnaire responses. The assessors assigned a score of 1 for each correct description of a symptom term or a score of 0 otherwise. The assessments were compared and discrepancies resolved by consensus.

The primary outcome of the study was the level of satisfaction with the checklists. This was determined by computing the mean SUS Score from the participant's SUS questionnaire responses as follows. First, each questionnaire item's score contribution was defined as a discrete score ranging from 0 to 4. If x_i represents the position on the 5-point Likert response scale of a single questionnaire item i , then the score contribution was $(x_i - 1)$ for positively worded items (odd-numbered items) and $(5 - x_i)$ for negatively worded items (even-numbered items) in the questionnaire [157]. Next, the overall SUS score of a single participant's responses was computed by multiplying the item score contributions by 2.5 such that the overall SUS scores range from 0 to 100 in 2.5-point increments. Lastly, the one-sample Student's t-test was used to test the research hypothesis that the mean SUS score was >68 , corresponding to above average usability.

The secondary outcome was the level of mental effort required to complete case scenarios which was described using the overall median and range of all SMEQ scores. The Wilcoxon signed rank test was used to test the research hypothesis that the overall median SMEQ was <20 , corresponding to "Not very hard to do". The research hypothesis that the SMEQ scores for the case scenarios were non-identical was tested using the Kruskal-Wallis rank sum test. The Mann-Whitney-Wilcoxon Test was used to test the research hypothesis that there was a difference in the SMEQ scores for each pair of case scenarios.

Time to case completion was analyzed using an approach similar to the one used for the SMEQ tests described above. Case completion rates were measured as the proportion of users who successfully completed each case scenario. For each case scenario completed by a participant, completion data was coded as a binary measure of success (1) or failure (0) based on the similarity of the participant's responses to the corresponding reference standard responses. The adjusted Wald' test was used to determine the 95% confidence interval of the case completion rates.

7.3. Results

7.3.1. Participant Characteristics

The characteristics of the 12 study participants are shown in Table 7.2. Seven of the 12 participants were male, and all participants were above 35 years. Ten participants had a college-level education. Eight participants were peer counselors and educator, while 4 participants were retention and outreach workers. The median work experience was 9 years. Three participants reported prior experience using checklists. Most participants had an acceptable knowledge of common antiretroviral toxicity symptoms. There were no significant differences in usability findings between the subgroups defined by the participant characteristics. Consequently, the findings reported in this study were based on analysis of data from all the 12 participants.

7.3.2. Usability Findings

Figure 7.3 illustrates the participant's responses to the SUS questionnaire. The SUS showed a mean usability score of 72.3 (95% CI, 67.6 to 77.0, p-value <0.001). The observed data provided enough evidence to reject the null hypothesis and conclude that the true mean SUS score was >68 (p-value = 0.035), implying above-average usability [157]. The mental effort associated with each case is illustrated in Figure 7.4. The SMEQ showed an overall median mental effort of 10 (Range, 0 to 85). There was enough evidence to conclude that the overall median SMEQ score was <20 (p-value <0.001) implying that the task was "Not very hard to do". The SMEQ scores for Case 1, which was first to be attempted by all participants, were higher than the scores for the rest of the cases. Case 4, which was the most task-intensive, also received high SMEQ scores. A Kruskal-Wallis p-value of 0.005 suggested that the mental effort for different cases was non-identical. The Mann-Whitney-Wilcoxon test confirmed statistical differences in mental effort in 3 comparisons involving Case 5 and 1 comparison involving Case 3 (Table 7.3).

Table 7.2: Characteristics of Usability Study Participants (N=12)

| Variable | N (%) |
|-----------------------------------|-----------------|
| Gender | |
| Female | 5 (42%) |
| Male | 7 (58%) |
| Age | |
| 35 to 44 years | 5 (42%) |
| 45 to 54 years | 5 (42%) |
| 55 to 64 years | 2 (16%) |
| Level of Education | |
| Secondary School | 1 (8%) |
| College Certificate | 4 (33%) |
| College Diploma | 6 (50%) |
| University Degree | 1 (8%) |
| Current Role | |
| Peer Counseling & Education | 8 (67 %) |
| Retention and Outreach | 4 (33 %) |
| Work Experience in Years | |
| Median(IQR) | 7 (5-11) |
| Prior Experience Using Checklists | |
| Yes | 3 (25%) |
| No | 9 (75%) |
| Symptom Knowledge Score | |
| Median (IQR) | 80% (77.5%-90%) |

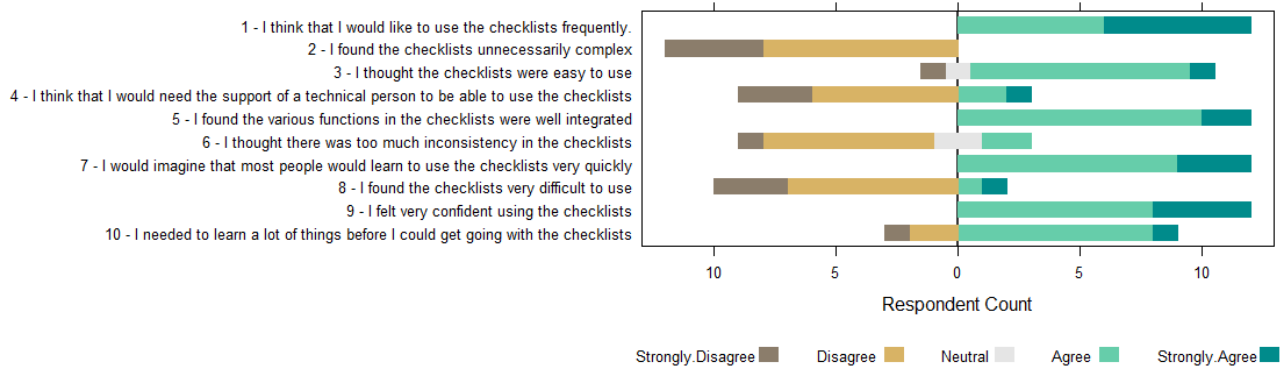


Figure 7.3: Diverging stacked bar chart of responses of the 10 SUS Likert-items

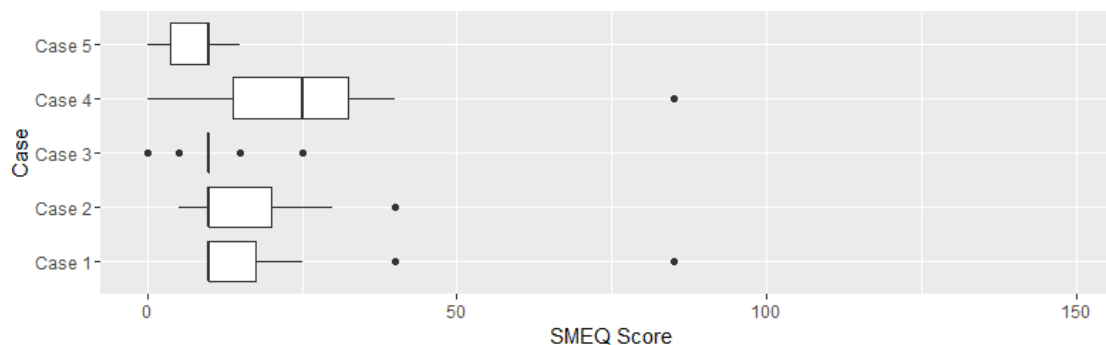


Figure 7.4: Mental effort associated with the 5 checklist documentation case scenarios.

Table 7.3: Differences in SMEQ and in Time to Case Completion between Case Scenarios

| Pair | SMEQ Score | | Time to Case Completion (Seconds) | |
|-----------------|---------------------|---------|-----------------------------------|---------|
| | Difference (95% CI) | p-value | Difference (95% CI) | p-value |
| Case 1 & Case 2 | 0 (-5 to 5) | 0.894 | 180 (0 to 420) | 0.039* |
| Case 1 & Case 3 | 0 (0 to 10) | 0.12 | 180 (0 to 360) | 0.036* |
| Case 1 & Case 4 | -5 (-15 to 0) | 0.2 | 0 (-180 to 180) | 0.977 |
| Case 1 & Case 5 | 5 (0 to 15) | 0.012* | 240 (60 to 480) | 0.011* |
| Case 2 & Case 3 | 5 (0 to 15) | 0.182 | 0 (-120 to 120) | 0.977 |
| Case 2 & Case 4 | -5 (-20 to 5) | 0.177 | -180 (-300 to -60) | 0.002* |
| Case 2 & Case 5 | 5 (0 to 15) | 0.026* | 60 (-60 to 180) | 0.26 |
| Case 3 & Case 4 | -15 (-25 to 0) | 0.016* | -180 (-300 to -60) | 0.006* |
| Case 3 & Case 5 | 0 (0 to 10) | 0.334 | 60 (-60 to 180) | 0.317 |
| Case 4 & Case 5 | 15 (5 to 25) | 0.002* | 240 (120 to 360) | 0.001* |

The times to case completion results are illustrated in Figure 7.5. The overall median time to case completion was 360 seconds (Range, 120 to 1560). The Kruskal-Wallis test indicated that the time taken to accomplish different cases was non-identical (p-value =0.001). The Mann-Whitney-Wilcoxon test confirmed that statistically significant difference in time to case completion comparisons involving Case 1 and Case 4 (Table 7.3). The binary case completion rates ranged from 7% to 78% and appeared to vary with the number of symptoms-to-toxicity mappings that had to be identified (Table 7.4). For example, Case 5 which only had 2 symptoms and 1 possible adverse reaction was completed by 10 of the 12 participants, while no participant successfully completed Case 4 which had 6 symptoms mapped to 4 possible adverse reactions via 16 mappings.

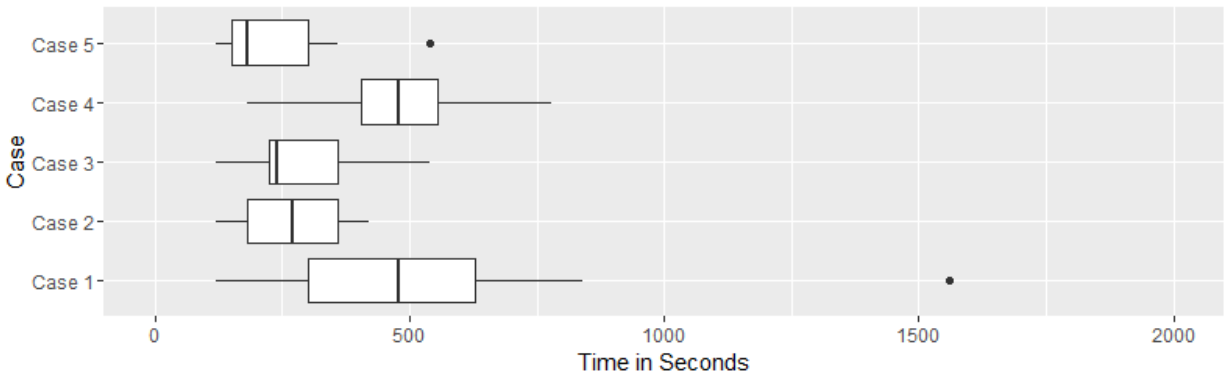


Figure 7.5: Time to case completion associated with 5 checklist documentation case scenarios

Table 7.4: Case Completion Rates with Adjusted Wald Confidence Intervals

| Task | Symptoms | Toxicities | Mappings | Completion Rate (95% CI) |
|--------|----------|------------|----------|--------------------------|
| Case 1 | 5 | 3 | 6 | 57%(32% to 80%) |
| Case 2 | 3 | 2 | 5 | 71% (46% to 92%) |
| Case 3 | 5 | 2 | 7 | 28%(9% to 54%) |
| Case 4 | 6 | 4 | 16 | 7% (0% to 22%) |
| Case 5 | 2 | 1 | 2 | 78%(54% to 97%) |

7.3.3. Error Analysis

The cause-of-error analysis revealed two main causes of errors that inform the redesign of the checklists. First, transcription errors were introduced by the presence of concepts described on the checklist using terms that looked similar and were possibly confusing to participants (Table 7.5). For example, some participants confused the concept *muscle pain* and *muscle weakness* and checked both entries for the same vignette excerpts. Similarly, the concept *nausea* which was described using the term *feeling like vomiting (nausea)* on the checklist, was confused with the term *vomiting*. Interestingly, this observation seems to contradict the perspectives of the professional provider about language as a barrier to the provision of monitoring services (Chapter 3). Second, and perhaps more consequential, a majority of the errors that were associated with low case completion rates were introduced through mistakes committed during the manual mapping and tallying of identified symptoms to the possible adverse reactions.

Table 7.5: Example of Concept-Related Sources of Transcription Errors

| Vignette Text Excerpt | Term Selected | Correct Term | Error Counts |
|--|---|---------------------|---------------------|
| I noticed a rash on my trunk and arm | Fat accumulation in the trunk of the body | Rash | 1 |
| I started having muscle pain | Muscle weakness | Muscle Pain | 2 |
| I have also been vomiting | Feeling like vomiting (Nausea) | Vomiting | 2 |
| ...and feeling like I have a fever | Generally feeling sick | Fever | 1 |
|and diarrhea. | Pale Stools | Diarrhoea | 1 |
| My muscles have also been feeling weak | Feeling tired | Muscle weakness | 1 |
| My muscles have also been feeling weak | Muscle pain | Muscle weakness | 1 |

7.4. Discussion

The findings of this study suggest that peer health workers in an underserved setting are likely to find the use of checklists for the documentation of antiretroviral toxicities as generally satisfactory and easy to use. The SUS showed a mean usability score of 72.3 which corresponds to above average usability. The SMEQ showed an overall median mental effort of 10, implying that peer health workers found the use of the checklist to be easy. The median time to case completion was 6 minutes. Interestingly, although there was a general consensus among the peer health workers that the checklists were satisfactory and easy to use, the case completion rates for relatively complex case scenarios was low. Errors in the documentation process were traceable to slips and mistakes in the interpretation of concepts described in the checklists, and in mapping symptoms to adverse drug reactions.

The two sources of errors yielded redesign and implementation recommendations. First, it will be useful to avoid the presence of potentially confusing, yet distinct concept descriptions such as *muscle pain* and *muscle weakness* in the checklists. The use of single pre-coordinated concepts such as *nausea and vomiting* could also be considered. Alternatively, the symptoms in the checklist

could be grouped using meaningful categories such as by body systems (e.g., head and neck symptoms vs. abdominal symptoms) to limit potential confusion. Additionally, the users of the checklists could be adequately trained to ensure that they are knowledgeable with respect to terminology used in the checklists. Second, mapping and tallying counts of symptoms associated with possible adverse reactions manually should be reconsidered as this is only feasible for less-complex mappings. A plausible alternative to the manual mapping requirement is the use of electronic checklists that automatically update possible adverse reaction counts as symptoms are checked off. However, this approach was not investigated in this study and is a suitable subject for future research.

Checklists are tools that could be used to standardize the documentation of clinical care. However, the use of standardized checklists as a formal approach to monitoring adverse drug reactions has primarily been limited to few specific clinical domains such as psychiatry [24] and diabetes [25]. This study not only demonstrated the plausibility of extending the use of checklists to the monitoring of adverse drug reactions in HIV but also attempted to validate their usability among non-mainstream lay care providers whom could be crucial in solving documentation challenges in underserved settings. Additionally, this research demonstrates the application of quantitative methods for measuring usability.

This study had several limitations. First, only 5 case scenarios were used in the usability testing, possibly introducing bias in the selection of case scenarios and variability in the results of the study. However, appropriate statistical analyses were used to ensure the correct interpretation of the findings. Second, the results of this study should be interpreted with caution as it is not possible to ascertain the honesty of the participants or the factuality of the information they provided when responding to the SMEQ and SUS questionnaires. Third, participants hailed from one clinical

setting, and it is, therefore, plausible that the results cannot be effectively generalized beyond the study setting without additional research.

7.5. Conclusions

The findings of this study suggest that peer health workers perceive computer-generated checklists for screening antiretroviral toxicity symptoms as satisfactorily useful and easy to use. However, measures should be taken to minimize possible errors in documentation. Future research should focus on evaluating the practical feasibility and impact of using peer health workers as documentation scribes in clinical care.

7.6. Appendixes

Appendix 7.1: Demographics Questionnaire

DEMOGRAPHICS QUESTIONNAIRE

Please attempt all questions in the Questionnaire

All answers are strictly confidential and will be used for the purposes of research only

Question 1: What is your age group?

☐ 18 to 24 years ☐ 25 to 34 years ☐ 35 to 44 years ☐ 45 to 54 years ☐ 55 to 64 years ☐ Age 65 or older

Question 2: What is your gender?

☐ Male ☐ Female

Question 3: What is your highest degree or education level?

- ☐ Primary School
☐ Secondary School
☐ College Certificate in _____
☐ College Diploma in _____
☐ University Degree in _____
☐ Other: _____

Question 4: What is your current role at AMPATH?

Current Role: _____

Question 5: For how long have you worked in your current role at AMPATH?

Years: _____ Months: _____

Question 6: What previous roles have you played at AMPATH in the past?

Previous Roles: 1) _____
2) _____
3) _____

SYMPTOM KNOWLEDGE QUESTIONNAIRE

Please attempt all questions in the Questionnaire

All answers are strictly confidential and will be used for the purposes of research only

The following terms refer to side effects of antiretroviral medications. Please briefly define or describe each term. If you know a term but cannot define or describe it in English, please feel free to use Kiswahili:

- 1) Abnormal dreams: _____

- 2) Blisters: _____

- 3) Diarrhoea: _____

- 4) Difficulty in Swallowing: _____

- 5) Difficulty Sleeping: _____

- 6) Fainting: _____

- 7) Fatigue: _____

- 8) Rash: _____

- 9) Suicidal tendency: _____

- 10) Upper abdominal pain: _____

Appendix 7.3: Case Scenario Completion Example

I am Chris Wamukole, and my Id is A3425673. I have been using Combivir (Zidovudine and Lamivudine) and Nevirapine for four weeks now. Since last week, I have been feeling as if I am sick which is unusual for me. I also noticed a **rash** on my back, and I have been having a high **fever** for a few days now. My **eyes and palms started looking yellowish**, and I have been **vomiting** too. I stopped taking my medications last week because I thought they were making me sicker.

| Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) | | Wed Jul 12 2017 |
|---|-------------------------------------|---|
| First Name: <u>Chris</u> | Last Name: <u>Wamukole</u> | Person ID: <u>A3425673</u> |
| Check off signs/symptoms | | |
| Blisters on the skin (Malengelenge) | <input type="checkbox"/> | <p>Sign/Symptom counts</p> <p><u>4</u> Hepatotoxicity Nevirapine</p> <p><u>3</u> Hepatotoxicity Zidovudine</p> <p><u>5</u> Hypersensitivity Reaction Nevirapine</p> <p><u>1</u> Lactic Acidosis Zidovudine</p> <p>Lipoatrophy Zidovudine</p> <p>Myopathy Zidovudine</p> |
| Blisters, hives, or sores in the mouth (Malengelenge midomoni au kinywani) | <input type="checkbox"/> | |
| Dark-colored urine (Mkojo ulio na rangi nyeusi) | <input type="checkbox"/> | |
| Enlargement of the liver (Ini kuvimba) | <input type="checkbox"/> | |
| Fat loss in face (Upungufu wa mafuta usoni) | <input type="checkbox"/> | |
| Feeling cold in arms and legs (Baridi mikononi au miguuni) | <input type="checkbox"/> | |
| Feeling dizzy or lightheaded (Kizunguzungu) | <input type="checkbox"/> | |
| Feeling like vomiting (Hamu ya kutapika) | <input type="checkbox"/> | |
| Feeling tired (Uchovu) | <input type="checkbox"/> | |
| Fever (Kiwango cha juu cha joto (Homa)) | <input checked="" type="checkbox"/> | |
| Generally feeling sick (Hisi kuwa mgonjwa) | <input checked="" type="checkbox"/> | |
| Irregular heartbeat (Mdundo mmbaya wa moyo) | <input type="checkbox"/> | |
| Loss of appetite (Kukosa hamu ya kula) | <input type="checkbox"/> | |
| Loss of fat from arms and legs (Upungufu wa mafuta mikononi na miguuni) | <input type="checkbox"/> | |
| Muscle pain (Kuumwa na misuli) | <input type="checkbox"/> | |
| Muscle weakness (Udhaifu wa misuli) | <input type="checkbox"/> | |
| Pain in the joints (Kuumwa na viungo) | <input type="checkbox"/> | |
| Pain in the right upper abdomen (Maumivu ya tumbo upande wa kulia chini ya ubavu) | <input type="checkbox"/> | |
| Pale stools (Kinyesi nyeupe nyeupe) | <input type="checkbox"/> | |
| Rash (Vipele kwa ngozi) | <input checked="" type="checkbox"/> | |
| Redness or inflammation of the eyes (Uwekundu au uvimbe wa macho) | <input type="checkbox"/> | |
| Swelling of the face (kuvimba uso) | <input type="checkbox"/> | |
| Trouble breathing (Tatizo la kupumua) | <input type="checkbox"/> | |
| Vomiting (Kutapika) | <input checked="" type="checkbox"/> | |
| Yellowing of skin (Ngozi kuwa manjano) | <input checked="" type="checkbox"/> | |
| Yellowing of the eyes (Macho kuwa manjano) | <input checked="" type="checkbox"/> | |

Appendix 7.4: Subjective Mental Effort Question (SMEQ)



Instructions: Please draw a line through the numeric scale to indicate the mental effort you think you required to complete the present case.

Appendix 7.5: System Usability Scale (SUS) Questionnaire

1. I think that I would like to use the checklists frequently.

☐ Strongly Disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly Agree

2. I found the checklists unnecessarily complex.

☐ Strongly Disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly Agree

3. I thought the checklists were easy to use.

☐ Strongly Disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly Agree

4. I think that I would need the support of a technical person to be able to use the checklists.

☐ Strongly Disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly Agree

5. I found the various functions in the checklists were well integrated.

☐ Strongly Disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly Agree

6. I thought there was too much inconsistency in the checklists.

☐ Strongly Disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly Agree

7. I would imagine that most people would learn to use the checklists very quickly.

☐ Strongly Disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly Agree

8. I found the checklists very difficult to use.

☐ Strongly Disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly Agree

9. I felt very confident using the checklists.

☐ Strongly Disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly Agree

10. I needed to learn a lot of things before I could get going with the checklists.

☐ Strongly Disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly Agree

Chapter 8. Conclusions and Future Work

8.1. Summary of Findings

This dissertation research was informed by the view that to promote the point-of-care monitoring of antiretroviral toxicities in underserved settings that are characterized by health workforce challenges, it is critical to reconsider the current paradigm which requires clinicians to be the collectors, analyzers, and consumers of antiretroviral toxicity information all at the same time. Instead, better monitoring could be achieved by supporting clinician assessments of antiretroviral toxicities through the delegation of data collection tasks and the use of guideline-based antiretroviral toxicity decision support at the point of care. Consequently, this dissertation responded to several research questions that attempted to fill gaps in knowledge about leveraging task delegation and informatics solutions to overcome barriers associated with point-of-care monitoring of antiretroviral toxicities in underserved settings.

The research strategy adopted in this dissertation generated knowledge about antiretroviral toxicity monitoring in underserved settings. In particular, this dissertation produced empirical evidence about the motives and strategies for medication therapy management (MTM) services in underserved settings. It also identified key barriers and facilitators of antiretroviral toxicity monitoring within ambulatory HIV care workflows in underserved settings. Additionally, the dissertation described the objectives, process, and challenges associated with the construction of a software prototype implementing antiretroviral toxicity domain knowledge. It also provided evidence on the structure and behavior of the prototype's knowledge base. Lastly, the research provided previously unavailable empirical evidence about the perceptions of lay health workers on the use of checklists for the documentation of antiretroviral toxicities. A summary of the main findings of this dissertation vis-à-vis the research questions it asked is provided in Table 8.1 below.

Table 8.1: Summary of research questions and Key findings

| Question | Key Findings |
|--|--|
| What are the perspectives of healthcare providers based in an underserved setting on the motives and strategies for the provision of MTM services in such settings? | <ul style="list-style-type: none"> • Enhancement of medication adherence, safety and effectiveness is motivated by the desire to improve individual patient outcomes and to avert public health risks posed by suboptimal use of medications • Service delivery is influenced by the provider's perceptions of having the knowledge, skills, and time to provide the services adequately, and by the patient's willingness and ability to self-manage and engage in MTM processes • Strategies for overcoming workforce and patient engagement challenges are likely to require collaboration between professionals care providers and lay health workers |
| What constitutes the ambulatory HIV care workflow in an example of an underserved setting? | <ul style="list-style-type: none"> • Workflows are primarily designed to document care observations using structured encounter forms • Clinicians are the primary collectors, analyzers, and consumers of clinical data including those pertaining to antiretroviral toxicity |
| What are the barriers to and facilitators of point-of-care antiretroviral toxicity monitoring in underserved settings? | <ul style="list-style-type: none"> • Barriers can be pinpointed to processes involving the documentation and analysis of antiretroviral toxicity data. These include clinician time and workload constraints, limitations in data collection form design, and the failure to capture the reasoning of clinicians. • Opportunities for improving data collection include the availability of peer health workers whom could take up data collection roles and considerable patient wait times that could be utilized for additional data collection. Opportunities for improving data analysis and interpretation include the adoption and use of electronic health records and clinical decision support in underserved settings |
| To what extent are the ingredient-condition relationships in a prototype knowledge base similar to those in existing drug safety knowledge bases? | <ul style="list-style-type: none"> • Up to 88% (75% through automated comparison and 13% through manual semantic similarity assessment) of paired ingredient-condition relationships extracted from clinical guidelines and current drug labels and implemented in a prototype knowledge base are equivalent to ingredient-condition relationships provided in existing drug safety evidence knowledge bases. |
| To what extent is the detection of antiretroviral toxicity by a prototype knowledge base comparable to the detection by human experts for a random sample of test cases? | <ul style="list-style-type: none"> • The difference in Jaccard distance between antiretroviral toxicity reports generated by the prototype and reports generated human experts was 0.112 (0.06 to 0.163, p-value <0.001) suggesting inferiority of the prototype in detecting possible antiretroviral toxicity associations from structured data. The reason for dissimilarities was attributable to inadequate domain coverage by the prototype. • The differences in the accuracy of reports between the prototype and human experts were not distinguishable |
| To what extent do lay peer health workers perceive checklists for screening antiretroviral toxicity symptoms as satisfactorily useful and easy to use? | <ul style="list-style-type: none"> • The SUS showed a mean usability score of 72.3 suggesting that lay peer health workers have above average satisfaction with the use of checklists for the documentation of antiretroviral toxicity symptoms. • The SMEQ showed an overall median mental effort of 10 (Range, 0 to 85) corresponding to "Not very hard to do", but ranging from "not at all hard to do" to "very hard to do". |

8.2. Conclusions

Overall, this dissertation demonstrates that the problem of inadequate antiretroviral toxicity monitoring during routine clinic visits in underserved settings could be mitigated by leveraging task shifting and knowledge-based clinical decision support to enhance information acquisition, information analysis, and decision-making. Such an endeavor would, however, require the combined effort of several stakeholders including patients, non-mainstream care providers such as peer health workers, clinicians, and informaticians, as well as considerable workflow process redesigns. Patients should be willing and able to actively participate in the antiretroviral toxicity monitoring activities, while care programs should direct efforts towards promoting patient engagement in care processes. More readily available personnel including lay health workers would need to take up new roles such as gathering and documenting patient information during clinical encounters. Concomitantly, clinicians should have the skills necessary for symptom-directed monitoring and would be required to focus on analyzing patient-reported data rather than on data collection. Informaticians should direct their efforts towards developing more effective workflow tools that support symptom-directed antiretroviral toxicity monitoring. A summary of the overall conclusions of the dissertation are discussed as follows.

Setting-specific barriers hinder the point-care monitoring of antiretroviral toxicity. As inferred from the findings of the study described in Chapter 3 of this dissertation, possible provider-related barriers to the antiretroviral toxicity monitoring include inadequate knowledge, skills, or time to provide the services. From the same study, it was also evident that stigma and passivity are important patient-related barriers which would hinder engagement in antiretroviral toxicity monitoring. In Chapter 4, workflow-specific barriers were pinpointed to processes

involving the documentation and analysis of patient-reportable and clinician-identified antiretroviral toxicity data.

Task shifting could be an essential strategy for improving point-of-care antiretroviral toxicity monitoring in underserved settings. The research conducted in this dissertation provided evidence to suggest that task shifting, defined as the delegation of clinical responsibilities from professionals to more readily available but less-skilled care providers, could be leveraged to improve point-of-care antiretroviral toxicity monitoring in underserved settings. In particular, task redistribution models in which professionals and lay health care providers work together are likely to succeed. Evidence in support of task shifting in this dissertation is as follows. The review of literature conducted in this dissertation (Chapter 2) identified task shifting as a universal strategy for mitigating workforce challenges in underserved settings. Task shifting also emerged as a strategy for enhancing medication adherence, safety, and effectiveness in underserved settings in the explorative study described in Chapter 3 of this dissertation. Chapter 4 of the dissertation describes a workflow analysis study from which task shifting roles in the form of peer counseling, patient education, and outreach could be identified. Lastly, the findings of the usability study described in Chapter 7 of the dissertation suggest that antiretroviral symptom data collection could be satisfactorily achieved through task shifting.

Point-of-care antiretroviral toxicity monitoring in underserved settings could potentially be enhanced using knowledge-based applications implementing care standard guidelines. In Chapter 4 of this dissertation, it was evident that key workflow barriers to the point-of-care monitoring of antiretroviral toxicities pertained to the inadequate documentation and analysis of antiretroviral toxicity data. Chapter 5 demonstrated how the identified workflow barriers could be mitigated through the construction of a knowledge based application system that supports

automated reasoning about antiretroviral medication, medication regimens, and toxicities. The findings of the study in Chapter 6 of the dissertation confirmed that knowledge-based applications have the potential to support automated detection of antiretroviral toxicities, risk factors and observations (signs, symptoms, and laboratory findings) from the analysis of structured patient records. On the other hand, the findings in Chapter 7 demonstrate that computer-generated checklists could be used to not only improve data collection but to do so using the task shifting approach.

8.3. Contribution to Informatics

This dissertation contributes to informatics in several ways. First, it demonstrated the application of the contextual design methodology as an approach for gaining insight into and modeling workflows based in underserved settings. This approach could be used by informaticians to understand drivers of suboptimal performance within clinical workflows in underserved settings and how informatics tools could be designed and integrated to address the identified barriers. The workflow analysis approach used in this dissertation also demonstrated that the rapid review of published literature targeting study settings in which workflows are investigated could be effective complements to the traditional approaches used to conduct workflow analyses.

Second, this dissertation investigated the extent to which antiretroviral toxicity domain knowledge could be implemented in a knowledge-based application to support point-of-care antiretroviral toxicity monitoring. In so doing, the dissertation described a systematic process for acquiring antiretroviral toxicity domain knowledge and representing the knowledge formally in an intuitive graph model that supports inference about toxicities from different levels of abstractions including regimens, ingredients, and clinical drugs. The model developed and the approach used are important resources for informatics research. Additionally, this dissertation research demonstrated

how the structure and behavior of independently-developed knowledge base applications could be systematically evaluated. In particular, the dissertation demonstrated how existing evidence knowledge bases could be used to validate the structure of independently developed prototypes. It also demonstrated how a reliable set of test cases for validating the behavior of prototypes could be generated from published case reports using a semi-automated process involving natural language processing and expert review.

Lastly, this dissertation demonstrated how quantitative standard usability tests could be applied to assess the satisfaction and mental effort associated with the completion of usability tasks. Particularly, and unlike a majority of usability testing that involve tech-savvy users using electronic interfaces, this dissertation contributes to the body of knowledge of usability testing by assessing usability as perceived by less tech-savvy peer health workers using low-tech paper-based checklists.

8.4. Contributions to Clinical Care

This dissertation contributes to clinical care in a variety of ways. It addressed the lack of research evidence on the provision of MTM services in underserved settings. This was achieved by triangulating the perspectives of care providers working in an example of an underserved setting to characterize the motives and strategies for improving medication adherence, safety, and effectiveness that are applicable in such settings. Accordingly, a major clinical contribution of this dissertation research is that it provides much-needed evidence on why MTM services are important in underserved settings, who needs such services, components required to deliver the services, and how the services can be delivered. This information is particularly important because the provision of MTM services is a relatively new paradigm that is yet to diffuse into underserved settings. For

example, stakeholders could compare different motives and strategies and identify the ones that are best aligned to their setting-specific needs.

Another important clinical implication of this dissertation research is that it provides analytic insight into the manner in which HIV workflows in underserved care settings operate. This dissertation research is one of the first to specifically visually illustrate models that describe the different dimensions of the ambulatory HIV care workflows in an example of an underserved setting. It is also one of the first research endeavors to describe specific workflow-related barriers to and opportunities for improving point-of-care monitoring of antiretroviral toxicities. The evidence generated from these workflow analyses could prove useful to HIV care programs and policymakers by informing the redesign of clinical workflows to improve point-of-care antiretroviral toxicity monitoring in underserved settings. Such undertakings would be particularly crucial in settings which lack the capacity to conduct stand-alone pharmacovigilance.

Additionally, this dissertation provides evidence in support of the integration of peer health workers into ambulatory HIV care workflows to assist with data collection tasks. This could have a direct impact on the manner in which care is delivered in underserved settings. While the approach could be useful in improving the data collection processes, HIV care programs would have to consider the tradeoffs between enhancing patient safety using this approach and mitigating the potential costs associated with additional monitoring.

Lastly, as part of this dissertation, a knowledge-based application prototype that has the potential to improve antiretroviral toxicity data collection and analysis was developed. With additional refinement, this prototype could prove useful as a clinical documentation resource, a decision-making aid, and a drug information repository for clinicians working in ambulatory HIV care workflows in underserved settings.

8.5. Limitations

This dissertation research had several general limitations. First, due to the shortcomings of the study designs employed in this research work, accurate causal inferences may not be made out of the studies conducted in the program of research. The findings of this dissertation should, therefore, be viewed as exploratory rather than confirmatory. Second, the qualitative designs involving self-reporting by human subjects in the program of research are subject to internal validity and reliability limitations. It is neither possible to prove the honesty of the participants and factuality of the information they provided, nor is it guaranteed that replicating the qualitative studies would generate similar findings. Third, due to time and resource constraints, the studies involving human subjects had small sample size. Although appropriate statistical analysis approaches were used, the inference from these studies may not be generalizable beyond the specific populations from which the participants were drawn. Fourth, the problem awareness studies (chapters 3 and 4) primarily focused on characterizing contextual barriers to and facilitators of antiretroviral monitoring. This approach inadvertently led to the inadequate investigation of the intrinsic perceptions of clinicians and patients on antiretroviral toxicity management. It is, therefore, possible that the findings of this study do not reflect the opinions of all healthcare stakeholders. Fifth, only one setting was used for the field studies. The choice of this site was based on familiarity with the setting and the fact it actively researches strategies for improving care delivery in underserved settings. However, being a large collaboration between different institutions, this setting may not be a true representation of other underserved settings. It is, therefore, plausible that findings of this study underestimate the true challenges of antiretroviral monitoring in underserved settings, and that solutions generated by this dissertation may not be

universally applicable. Lastly, focusing on antiretroviral toxicities limits the generalizability of the findings to other diseases or drug therapy problems.

8.6. Future Work

This dissertation research is generally exploratory and, therefore, raises a number of opportunities for future research. For example, this dissertation identified several broad strategies that could be used to improve medication adherence, safety, and effectiveness in underserved settings. Future research could investigate the feasibility and comparative effectiveness of these different strategies, especially with respect to the monitoring antiretroviral toxicities. Further research is also needed to delineate the workflow-related barriers and facilitators of antiretroviral toxicity monitoring that are intrinsic to human actors such as patients and clinicians. Additionally, this dissertation shed some light on the potential use of peer health workers as collectors of antiretroviral toxicity information via checklists. However, the usability investigations applied in the dissertation relied on written vignettes rather than real-life scenarios. Future research is, therefore, needed to assess the practical feasibility of peer health workers using checklists to document antiretroviral toxicity symptoms. Additional research is also needed to clarify whether the performance of peer health workers using checklists could be improved through interventions such as training and education. With respect to the development of the prototype created in this dissertation, additional testing of its performance when in actual clinical use is required. Also, future informatics research should focus on delineating ways in which the prototype deals with uncertainty and inadequate domain coverage. Lastly, the implementation of knowledge-based systems using traditional methods such as relational database systems could be complex and challenging. Future informatics research should investigate ways in which newer technologies such as graph database systems could be used to implement knowledge-based applications.

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